

Eric I. Abraham  
HILL WALLACK LLP  
21 Roszel Road  
Princeton, NJ 08540  
(609) 924-0808  
*Attorney for Defendants Dr. Reddy's  
Laboratories Inc., Dr. Reddy's Laboratories  
Ltd., and Sandoz Inc.*

Lisa J. Rodriguez  
Schnader Harrison Segal & Lewis LLP  
Woodland Falls Corporate Park  
220 Lake Drive East, Suite 200  
Cherry Hill, NJ 08002-5222  
(856) 482-5222  
*Attorneys for Defendant Pharmascience Inc.*

Theodora McCormick  
Lauren B. Cooper  
Robert Lufrano  
EPSTEIN BECKER & GREEN, P.C.  
150 College Road West, Suite 301  
Princeton, NJ 08540  
(609) 455-1540  
*Attorneys for Defendant Zydus  
Pharmaceuticals (USA) Inc.*

**UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY**

AMGEN INC.

Plaintiff,

v.

SANDOZ INC., et al.,

Defendants.

**Civil Action No. 18-11026 (MAS)(DEA)  
(consolidated)**

**FILED UNDER SEAL  
Contains Confidential Information**

**DEFENDANTS' PRETRIAL BRIEF**

**TABLE OF CONTENTS**

	<b>Page</b>
I. INTRODUCTION .....	1
II. BACKGROUND .....	3
A. Stereochemistry.....	3
B. Known Techniques to Obtain Stereomerically Pure Compounds.....	5
C. Polymorphism.....	5
D. The Prior Art Taught the Use of PDE4 Inhibitors to Treat Psoriasis .....	7
E. The Prior Art Taught That Thalidomide Analogues Are Potent PDE4 Inhibitors .....	9
F. Clinical Studies of Apremilast for the Treatment of Psoriasis .....	9
III. CLAIM CONSTRUCTION.....	10
IV. ARGUMENT .....	11
A. The '638 Patent .....	11
i. The Asserted Claims of the '638 Patent.....	11
ii. Prosecution History of the '638 Patent .....	12
iii. Priority Date.....	14
iv. Claims 3 and 6 Are Invalid As Anticipated.....	15
v. Claims 3 and 6 Are Invalid As Obvious.....	18
vi. Claims 3 and 6 Are Invalid under the Obviousness-Type Double Patenting Doctrine. ....	31
B. The '536 Patent .....	34
i. The Asserted Claim of the '536 Patent .....	36
ii. The Asserted Claim of the '536 Patent Is Not Entitled to a Priority Date Earlier Than March 20, 2002 .....	36
iii. The Asserted Claim of the '536 Patent Is Anticipated by the '358 Patent.....	37
iv. The Asserted Claim of the '536 Patent Would Have Been Obvious .....	38
v. The Asserted Claim of the '536 Patent Lacks Adequate Written Description.....	49
vi. The Asserted Claim of the '536 Patent Is Not Adequately Enabled .....	50
C. The '101 Patent .....	50
i. The Asserted Claims of the '101 Patent.....	53

ii.	The Asserted Claims of the '101 Patent Are Not Entitled to a Priority Date Earlier Than March 27, 2008 .....	55
iii.	The Asserted Claims of the '101 Patent Would Have Been Obvious to a POSA as of March 27, 2008.....	59
iv.	The Asserted Claims of the '101 Patent Would Have Been Obvious to a POSA as of March 20, 2002.....	61
v.	Other Prior Art Combinations Render Asserted Claims of the '101 Patent Obvious.....	63
vi.	No Objective Indicia of Nonobviousness .....	66
vii.	The Asserted Claims of the '101 Patent Are Invalid under the Obviousness Type Double Patenting Doctrine. ....	66
viii.	Amgen Cannot Establish that Zydus's Proposed ANDA Product Infringes the '101 Patent.....	69
D.	The '541 Patent.....	73
i.	The Asserted Claims of the '541 Patent.....	74
ii.	The Asserted Claims of the '541 Patent Would Have Been Obvious .....	75
iii.	No Objective Indicia of Nonobviousness .....	85
iv.	The Alleged Evidence of "Unexpected Results" Presented During Prosecution of the '541 Patent Does Not Support the Non-Obviousness of the Asserted Claims.....	85
v.	Amgen Cannot Prove that Pharmascience Will Infringe Claims 2, 19 or 21 of the '541 Patent.....	86
E.	The '283 Patent .....	97
i.	The Asserted Claims of the '283 Patent.....	97
ii.	The '283 patent is invalid as anticipated and/or obvious.....	98
iii.	The '052 publication anticipates claims 2 and 27 of the '283 patent.....	99
iv.	Claims 2 and 27 of the '283 Patent Would Have Been Obvious Over the '052 Publication in View of Fieser, Guillory, and Byrn 1994 and the Knowledge of a POSA. ....	101
v.	Claims 2 and 27 of the '283 Patent Would Have Been Obvious Over the '358 Patent in view of Byrn 1995, in Further View of Guillory and Byrn 1994 and the Knowledge of a POSA.....	103
V.	CONCLUSION.....	105

**TABLE OF AUTHORITIES**

	<b>Page(s)</b>
<b>Cases</b>	
<i>Abbvie Inc. v. Mathilda &amp; Terence Kennedy Inst. of Rheumatology Tr.</i> , 764 F.3d 1366 (Fed. Cir. 2014).....	33, 34, 52, 66, 67
<i>Acorda Therapeutics, Inc. v. Roxane Labs., Inc.</i> , 903 F.3d 1310 (Fed. Cir. 2018).....	29, 36, 47
<i>Alcon Rsch. LTD v. Apotex, Inc.</i> , 687 F.3d 1362 (Fed. Cir. 2012).....	12
<i>Allergan, Inc. v. Sandoz Inc.</i> , 796 F.3d 1293 (Fed. Cir. 2015).....	58
<i>ALZA Corp. v. Andrx Pharm., LLC</i> , 603 F.3d 935 (Fed. Cir. 2010).....	50
<i>Amgen Inc. v. Amneal Pharm. LLC</i> , 945 F.3d 1368 (Fed. Cir. 2020).....	87
<i>Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.</i> , 598 F.3d 1336 (Fed. Cir. 2010).....	56, 57, 58
<i>Aventis Pharma Deutschland GmbH v. Lupin, Ltd.</i> , 499 F.3d 1293 (Fed. Cir. 2007).....	21, 22, 23
<i>Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.</i> , 713 F.3d 1369 (Fed. Cir. 2013).....	35, 48
<i>Beckman Instruments Inc. v. LKB Produkter AB</i> , 892 F.2d 1547 (Fed. Cir. 1989).....	25
<i>Biovail Labs. Int’l SRL v. Abrika, LLLP</i> , No. 04-61704, 2006 WL 6111777 (S.D. Fla. Aug. 24, 2006) .....	87
<i>Classified Cosmetics, Inc. v. Del Labs., Inc.</i> , No. 03-4818, 2004 WL 5645578 (C.D. Cal. June 14, 2004).....	87
<i>Coleman v. Dines</i> , 754 F.2d 353 (Fed. Cir. 1985).....	37
<i>Constant v. Advanced Micro-Devices Inc.</i> , 848 F.2d 1560, 1570 (Fed. Cir. 1988).....	15

<i>Cooper v. Goldfarb</i> , 154 F.3d 1321 (Fed. Cir. 1998).....	14
<i>Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.</i> , 424 F.3d 1293 (Fed. Cir. 2005).....	88
<i>Depomed, Inc. v. Sun Pharma Global FZE</i> , Civ. No. 11-3553 (JAP), 2012 WL 3201962 (D.N.J. Aug. 3, 2012) .....	87
<i>DSU Med. Corp. v. JMS Co.</i> , 471 F.3d 1293 (Fed. Cir. 2006) (en banc).....	88
<i>Ferring B.V. v. Watson Lab'ys, Inc.-Fla.</i> , 764 F.3d 1401, 1408 (Fed. Cir. 2014).....	69
<i>Forest Labs., Inc. v. Ivax Pharms. Inc.</i> , 501 F.3d 1263 (Fed. Cir. 2007).....	13
<i>Fujitsu Ltd. v. Netgear Inc.</i> , 620 F.3d 1321 (Fed. Cir. 2010).....	88
<i>Galderma Labs., L.P. v. Tolmar, Inc.</i> , 737 F.3d 731 (Fed. Cir. 2013).....	3, 43, 77, 85
<i>Genentech, Inc. v. Hospira, Inc.</i> , 946 F.3d 1333 (Fed. Cir. 2020).....	48
<i>Gentry Gallery, Inc. v. Berkline Corp.</i> , 134 F.3d 1473 (Fed. Cir. 1998).....	49
<i>Gilead Scis., Inc. v. Natco Pharma Ltd.</i> , 753 F.3d 1208 (Fed. Cir. 2014).....	31
<i>Glaxo, Inc. v. Novopharm, Ltd.</i> , 110 F.3d 1562 (Fed. Cir. 1997).....	70, 73
<i>Hoffman-La Roche Inc. v. Apotex, Inc.</i> , 748 F.3d 1326 (Fed. Cir. 2014).....	83
<i>Horizon Medicines LLC v. Alkem Labs Ltd.</i> , No. CV 18-1014-RGA, 2020 WL 7022591 (D. Del. Nov. 30, 2020).....	<i>passim</i>
<i>Hyatt v. Boone</i> , 146 F.3d 1348 (Fed. Cir. 1998).....	56
<i>HZNP Medicines LLC v. Actavis Labs. UT, Inc.</i> , 940 F.3d 680, 940 F.3d .....	88

<i>Imhaeuser v. Buerk</i> , 101 U.S. 647 (1879).....	86
<i>In re Adamson</i> , 275 F.2d 952 (C.C.P.A. 1960) .....	22
<i>In re Applied Materials, Inc.</i> , 692 F.3d 1289 (Fed. Cir. 2012).....	74, 76, 81
<i>In re Gershon</i> , 372 F.2d 535, 538 (C.C.P.A. 1967) .....	29
<i>In re Goodman</i> , 11 F.3d 1046 (Fed. Cir. 1993).....	50
<i>In re Gray</i> , 53 F.2d 520, 11 USPQ 255 (CCPA 1931).....	86, 92
<i>In re Huai-Hung Kao</i> , 639 F.3d 1057 (Fed. Cir. 2011).....	30, 46, 48
<i>In re Merck</i> , 800 F.2d 1091 .....	26
<i>In re Sebela Patent Litig.</i> , 2017 WL 3449054 (D.N.J. Aug. 11, 2017) .....	85
<i>In re Wands</i> , 858 F.2d 731 (Fed. Cir. 1988).....	50
<i>In re Young</i> , 927 F.2d 588 (Fed. Cir. 1991).....	42
<i>Jazz Photo Corp. v. ITC</i> , 264 F.3d 1094 (Fed. Cir. 2001).....	86
<i>Kennametal, Inc. v. Ingersoll Cutting Tool Co.</i> , 780 F.3d 1376 (Fed. Cir. 2015).....	17, 43
<i>KSR Int'l Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007).....	19, 22
<i>Laitram Corp. v. Rexnord, Inc.</i> , 939 F.2d 1533 (Fed. Cir. 1991).....	86
<i>Lockwood v. Am. Airlines, Inc.</i> , 107 F.3d 1565 (Fed. Cir. 1997).....	56, 57

<i>Los Angeles Biomedical Rsch. Inst. at Harbor-UCLA Med. Ctr. v. Eli Lilly &amp; Co.</i> , 849 F.3d 1049 (Fed. Cir. 2017).....	57
<i>Magna Electronics, Inc. v. TRW Automotive Holdings Corp.</i> , Nos. 1:12-cv-654, 1:13-cv-324, 2015 WL 11430786 (W.D. Mich. Dec. 10, 2015) .....	52, 67
<i>McCoy v. Heal Sys., LLC</i> , No. 2020-1484, 2021 WL 1235188 (Fed. Cir. Apr. 1, 2021) .....	15, 16
<i>Medichem, S.A. v. Rolabo, S.L.</i> , 437 F.3d 1157 (Fed. Cir. 2006).....	14
<i>Merck &amp; Co. v. Hi-Tech Pharmacal Co.</i> , 482 F.3d 1317 (Fed. Cir. 2007).....	53, 67
<i>Merck Sharp &amp; Dohme Corp. v. Amneal Pharms. LLC</i> , 881 F.3d 1376 (Fed. Cir. 2018).....	70
<i>Merck Sharp &amp; Dohme Corp. v. Teva Pharms. USA, Inc.</i> , 217 F. Supp. 3d 782 (D. Del. 2016).....	71
<i>Microsoft Corp. v. I4I Ltd. P'ship</i> , 564 U.S. 91 (2011).....	101
<i>Multilayer Stretch Cling Film Holdings, Inc., v. Berry Plastics Corp.</i> , 831 F.3d 1350 (Fed. Cir. 2016).....	87
<i>Muniauction, Inc. v. Thomson Corp.</i> , 532 F.3d 1318 (Fed. Cir. 2008).....	25
<i>Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.</i> , 166 F.3d 1190 (Fed. Cir. 1999).....	50
<i>Novartis AG v. Ezra Ventures LLC</i> , 909 F.3d 1367 (Fed. Cir. 2018).....	34, 53, 67
<i>Novartis AG v. Torrent Pharms. Ltd.</i> , 853 F.3d 1316 (Fed. Cir. 2017).....	25, 28, 53
<i>Novartis Farm Corp. v. West-Ward Pharms. Int'l Ltd.</i> , 923 F.3d 1051 (Fed. Cir. 2019).....	22
<i>Ohio Willow Wood Co. v. Alps S., LLC</i> , 735 F.3d 1333 (Fed. Cir. 2013).....	43
<i>Otsuka Pharm. Co., Ltd. v. Torrent Pharms. Ltd., Inc.</i> , 99 F. Supp. 3d 461 (D.N.J. 2015) .....	90

<i>Pfizer Inc. v. Teva Pharmaceuticals USA, Inc.</i> , 555 F. App'x 961 (2014) .....	17
<i>Pfizer, Inc. v. Apotex, Inc.</i> , 480 F.3d 1348 (Fed. Cir. 2007).....	<i>passim</i>
<i>Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.</i> , 843 F.3d 1315 (Fed. Cir. 2016).....	87
<i>PowerOasis, Inc. v. T-Mobile USA, Inc.</i> , 522 F.3d 1299 (Fed. Cir. 2008).....	50, 55
<i>PPG Industries v. Guardian Industries</i> , 156 F.3d 1351 (Fed. Cir. 1998).....	94
<i>Proctor &amp; Gamble Co. v. Nabisco Brands, Inc.</i> , 711 F. Supp. 759 (D. Del. 1989).....	17, 18
<i>Prometheus Labs., Inc. v. Roxane Labs., Inc.</i> , 805 F.3d 1092 (Fed. Cir. 2015).....	30
<i>Purdue Pharma L.P. v. Faulding Inc.</i> , 230 F.3d 1320 (Fed. Cir. 2000).....	49
<i>Raytheon Techs. Corp. v. Gen. Elec. Co.</i> , 993 F.3d 1374 (Fed. Cir. 2021).....	25
<i>Sanofi-Synthelabo v. Apotex, Inc.</i> , 550 F.3d 1075 (Fed. Cir. 2008).....	13
<i>Santarus Inc. v. Par Pharm. Cos. Inc.</i> , 945 F.3d 1184 (Fed. Cir. 2019).....	59, 61
<i>Santarus, Inc. v. Par Pharm., Inc.</i> , 694 F.3d 1344 (Fed. Cir. 2012).....	42
<i>Sciele Pharma Inc. v. Lupin Ltd.</i> , 684 F.3d 1253 (Fed. Cir. 2012).....	19
<i>Sherwin-Williams Co. v. PPG Indus., Inc.</i> , No. CV 17-1023, 2021 WL 211497 (W.D. Pa. Jan. 21, 2021).....	18
<i>Shire LLC v. Amneal Pharmaceuticals, LLC</i> , 2014 WL 2861430 (D.N.J. 2014) .....	90
<i>SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.</i> , 225 F.3d 1349 (Fed. Cir. 2000).....	23

<i>Sing v. Brake</i> , 222 F.3d 1362 (Fed. Cir. 2000).....	37
<i>SmithKline Beecham Corp. v. Apotex Corp.</i> , 98 C 3852, 2002 WL 1613724 (N.D. Ill. July 17, 2002) .....	71
<i>Takeda Pharm. U.S.A. Inc. v. West-Ward Pharm. Corp.</i> , 785 F.3d 625 (Fed. Cir. 2015).....	90
<i>Vita-Mix Corp. v. Basic Holding, Inc.</i> , 581 F.3d 1317 (Fed. Cir. 2009).....	91, 95
<i>Zenith Labs., Inc. v. Bristol-Myers Squibb Co.</i> , 19 F.3d 1418 (Fed. Cir. 1994).....	72

#### **Statutes**

35 U.S.C. § 102.....	100
35 U.S.C. § 112.....	<i>passim</i>
35 U.S.C. § 271(c) .....	88
35 U.S.C. § 282(a) .....	101, 103

#### **Other Authorities**

37 C.F.R. § 1.56.....	101, 103
MPEP § 211.05 .....	32
MPEP § 2701 .....	32

## TABLE OF ABBREVIATIONS

Amgen	Plaintiff Amgen Inc.
Celgene	Celgene Inc.
Defendants	Defendants Dr. Reddy's Laboratories Inc., Dr. Reddy's Laboratories Ltd., Pharmascience Inc., Sandoz Inc., and Zydus Pharmaceuticals (USA) Inc.
DRL	Dr. Reddy's Laboratories Inc. and Dr. Reddy's Laboratories, Ltd.
Pharmascience	Pharmascience Inc.
Sandoz	Sandoz Inc.
Zydus	Zydus Pharmaceuticals (USA) Inc.
DTX	Defendants' trial exhibit
JTX	Joint trial exhibit
FDA	U.S. Food and Drug Administration
PTO	U.S. Patent and Trademark Office
PTE	Patent Term Extension
PTA	Patent Term Adjustment
API	Active Pharmaceutical Ingredient
Apremilast	(+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisoindoline-1,3-dione
PDE	Phosphodiesterase enzyme
PDE4	Phosphodiesterase enzyme 4
TNF $\alpha$ or TNF- $\alpha$	Tumor necrosis factor $\alpha$
cAMP	Adenosine 3',5'-cyclic monophosphate
'358 patent	U.S. Patent No. 6,020,358

WO '606	WO 01/34606
Takeuchi	Takeuchi et al., "(R)- and (S)-3-Fluorothalidomides: Isosteric Analogues of Thalidomide," <i>Organic Letters</i> , 1(10), 1571-73 (1999)
Dyke 1999	Dyke et al., "The therapeutic potential of PDE4 inhibitors," <i>Expert Opin. Invest. Drugs</i> , 8(9): 1301-25 (1999)
Marriott 2001	Marriott et al., "Immunotherapeutic and antitumor potential of thalidomide analogues," <i>Expert Opinion on Biological Therapy</i> , 1(4): 675-82 (2001)
Muller 1998	Muller et al., "Thalidomide Analogs and PDE4 Inhibition," <i>Bioorganic &amp; Medicinal Chemistry</i> , 8: 2669-74 (1998)
Papp 2012	Papp et al., "Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial," <i>Lancet</i> , 738-46 (2012)
Schett 2012	Schett et al., "Oral Apremilast in the Treatment of Active Psoriatic Arthritis," <i>Arthritis &amp; Rheumatism</i> , 64(10): 3156-67 (2012)
ICH Guidelines	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, <i>Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances</i> (1999)
'052 Publication	U.S. Patent Publication No. 2003/0187052
'049 Publication	WO 2003/080049
Brittain 1997	Brittain, H.G., "Spectral Methods for the Characterization of Polymorphs and Solvates," <i>Journal of Pharmaceutical Sciences</i> (1997)

Brittain 1999	D. J.W. Grant, <i>Theory and Origin of Polymorphism</i> , and H.G. Brittain, <i>Methods for the Characterization of Polymorphs</i> , Polymorphism in Pharmaceutical Solids, Vol. 95 (H. Brittain ed., 1999)
Byrn 1995	S. R. Byrn et al., "Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations," <i>Journal Pharmaceutical Research</i> , 12(7): 945-54 (1995)
Byrn 1999	S.R. Byrn et al., <i>Solid-State Chemistry of Drugs</i> (2d ed.) (1999)
Guillory	J. K. Guillory, <i>Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids</i> , Polymorphism in Pharmaceutical Solids, Vol. 95 (H. Brittain ed., 1999)
ICH 1994	ICH Harmonised Tripartite Guideline, Dose-Response Information to Support Drug Registration (Mar. 10, 1994)
'515 application	U.S. Provisional Application No. 60/366,515
Pathan 2012	Pathan et al., "Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in ankylosing spondylitis," <i>Ann. Rheum. Dis.</i> , 0:1-6 (2012)
NCT '092	Clinical Trial No. NCT00456092, "A Phase II, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Efficacy and Safety Study of CC-10004 in Subjects with Active Psoriatic Arthritis"
Kavanaugh 2014	Kavanaugh et al., "Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor," <i>Ann. Rheum. Dis.</i> , 73: 1020-26 (2014)

## I. INTRODUCTION

This case concerns five follow-on patents that plaintiff Amgen asserts against generic pharmaceutical manufacturers in an attempt to extend its monopoly over a decade after the expiration of its original patent related to the active drug substance, apremilast, which is marketed under the brand name Otezla®. Amgen should not be allowed to keep affordable generic alternatives off the market because its predecessor in interest, Celgene, created invalidating prior art and made critical admissions while designing Otezla®'s patent thicket. As a result, Celgene dedicated the claimed inventions to the public. Amgen cannot now rescind the public's access.

Defendants are seeking FDA approval to market apremilast tablets for the treatment of moderate to severe psoriasis, one of the same approved indications of Otezla®. Celgene sued Defendants alleging infringement of claims 3 and 6 of U.S. Patent No. 7,427,638 ("the '638 patent"), claim 6 of U.S. Patent No. 8,455,536 ("the '536 patent"), claims 1 and 15 of U.S. Patent No. 7,893,101 ("the '101 patent"), and claims 2, 19, and 21 of U.S. Patent No. 10,092,541 ("the '541 patent") (collectively, the "Asserted Claims" of the "Patents-in-Suit"). Subsequently, Amgen acquired the Patents-in-Suit and the NDA for Otezla® and stepped into the shoes of Celgene as plaintiff.

Defendants allege that the Asserted Claims of the '638, '536, '101, and '541 patents are invalid and therefore Defendants cannot be liable for infringement. Defendants will present clear and convincing evidence that all of the Asserted Claims are invalid for anticipation, obviousness, obviousness-type double patenting, and/or lack of written description and enablement. Defendant Pharmascience also asserts that it has not infringed, and will not infringe, the asserted claims of the '541 patent and that Amgen will be unable to prove its infringement allegations. Defendant Zydus will also explain why its proposed ANDA products do not infringe the asserted claims of the '101 patent.

Amgen also sued Zydus alleging infringement of claims 2 and 27 of U.S. Patent No. 8,093,283 (“the ’283 patent”). Zydus alleges that the asserted claims of the ’283 patent are invalid and therefore Zydus cannot be liable for infringement. Zydus will present clear and convincing evidence that the asserted claims of the ’283 patent are invalid for anticipation and/or obviousness.

When Defendants filed their respective Abbreviated New Drug Applications (ANDAs) in 2018, the ’358 patent was listed in the FDA’s Orange Book as a patent claiming the drug, or the method of using the drug, in Otezla®—*i.e.*, apremilast. Defendants each filed Paragraph III certifications to the ’358 patent in their respective ANDAs, as the patent would be expiring that same year. The ’358 patent claims a method of inhibiting PDE4 in a mammal by administering an effective amount of a compound according to a Formula I. Example 12 of the ’358 patent discloses the racemic mixture that is equal parts apremilast ((+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisindoline-1,3-dione) and the mirror isomer of apremilast ((-)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisindoline-1,3-dione). The ’358 patent also teaches that both racemates and individual isomers are within the scope of that invention, and that isomers can be obtained “substantially free of the other, *i.e.*, in a form having an optical purity of >95%,” by using chromatography or chiral acid salt formation. (DTX-174 (’358 patent) at 8:64-9:12.)

The prior art ’358 patent further provides therapeutically-effective doses and dosage forms for apremilast. The ’358 patent teaches that apremilast could be administered orally in the form of a tablet or capsule, “containing from 1 to 100 mg of drug per unit dosage,” as part of a “single or multiple dosage regimen.” (*Id.* at 9:22-24; 52-60.) The prior art thus overlaps with the doses in the Asserted Claims. “Where there is a range disclosed in the prior art, and the claimed invention

falls within that range, the burden of production falls upon the patentee to come forward with evidence” of secondary considerations of nonobviousness. *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 737 (Fed. Cir. 2013). Here, Amgen has not asserted any teaching away or unexpected results from administering the claimed doses of apremilast.

The '358 patent is also a “blocking patent”—the practice of any of the Asserted Claims would infringe one or more claims of the '358 patent. As of at least the 2002 priority date, a POSA would have been aware of the '358 patent, and it would have deterred unlicensed third parties from developing pharmaceutical compositions of stereomerically pure apremilast for the treatment of psoriasis.

By the time the '541 patent was effectively filed in 2014, there is no dispute that apremilast was already known and disclosed in the prior art, as were methods of using apremilast for treating patients with psoriasis. Amgen will argue that the allegedly inventive feature of this patent is the particular titration schedule recited in the asserted claims. Yet the evidence will show that the claimed titration scheme is simply a routine optimization over the prior art Papp 2012 study sponsored by Celgene. In short, there is nothing novel about the '541 patent, which serves as yet another example of Amgen's improper attempts to further extend its market exclusivity for Otezla®.

## **II. BACKGROUND**

### **A. Stereochemistry**

Apremilast is a chiral compound. An object or a system is chiral if it is distinguishable from its mirror image; that is, it cannot be superimposed onto it. Human hands are perhaps the most universally recognized example of chirality. The left hand is a non-superimposable mirror image of the right hand; no matter how the two hands are oriented, it is impossible for all the major features of both hands to coincide across all axes. “Enantiomers,” is a term used to describe a

mirror image pair of two chiral compounds. Enantiomers contain all the same atoms and bonds, but these atoms and bonds are spatially arranged such that they are mirror images of each other and are not superimposable. Enantiomers have the same physical and chemical properties, except for the direction in which they rotate a plane of polarized light, which they reason enantiomers are also referred to as optical isomers. A 50:50 mixture of two enantiomers is known as a “racemic mixture” or a “racemate.”

The '638 and '536 patents are directed to this characteristic of apremilast, which falls in the category of “stereochemistry.” The specification states that “[t]he invention particularly relates to the (+) enantiomer of 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisoindoline-1,3-dione. This compound is believed to have increased potency and other benefits as compared to the racemate.” (JTX-3 ('638 patent) at 3:23-29; *see also id.* at 13:49-56 (explaining that stereomerically pure apremilast provides an improved therapeutic effectiveness over the racemic mixture.))

In the field of pharmaceuticals, it has been well known since long before 2002 that stereochemistry can affect a molecule's fit within a biological receptor in the human body—which can affect the efficacy of the molecule. This is because biological molecules have orientations within 3-dimensional space, which alters whether any particular molecule may fit into a receptor like a lock and key. The analogy of enantiomers as right hand and left hand mirror images can show how enantiomers fit differently within a receptor or pass through a column that separates the two enantiomers. A right-handed person (*i.e.*, the active drug enantiomer) can only shake hands with another right hand (*i.e.*, the drug receptor) but not with a left hand because there is no “fit” or “lock” between the right hand of one person and the left hand of another. Because biological receptors (such as those contained in enzymes) are themselves chiral, there are many examples of

enantiomeric pharmaceuticals.

#### **B. Known Techniques to Obtain Stereomerically Pure Compounds**

Well before the priority date here, people of skill in the art understood what enantiomers and racemic mixtures were and were able to separate the two enantiomers from a racemic mixture into a “stereomerically pure” form of the enantiomer or to independently synthesize one of the two enantiomers. Moreover, since at least 1992, FDA has recommended that drug companies who are investigating racemic mixtures also separate and investigate each enantiomer to determine its properties. (DTX-119 at 2-3.)<sup>1</sup> FDA’s policy and guidance documents arise from the understanding that each enantiomer in a racemic mixture may differ in potency and toxicity. (*Id.*)

The specification of the ’638 patent admits that techniques for separating or synthesizing enantiomers of a racemic mixture, including apremilast, were well known: “[Apremilast] can be isolated from the racemic compound by techniques known in the art. Examples include, but are not limited to, the formation of chiral salts and the use of chiral or high performance liquid chromatography ‘HPLC’ and the formation and crystallization of chiral salts.” (JTX-3 (’638 patent) at 9:13-17.)

A number of common techniques were available to a POSA to obtain stereomerically pure enantiomers before the priority date of the ’638 patent. Several of these techniques, such as chiral chromatography, are taught in the prior art, including Celgene’s own ’358 patent.

#### **C. Polymorphism**

The ’101 patent is directed to what is called a “polymorph” or “crystalline form” of apremilast. Solid compounds may be amorphous or crystalline. Crystalline compounds have

---

<sup>1</sup> For clarity and consistency, the pin cites to non-patent references throughout this document refer to the DTX-stamped page numbers rather than the original document page numbers.

structural units (referred to as “unit cells”) that are repeated regularly in three dimensions in space. (See DTX-458 (Vippagunta) at 3.) Crystalline materials exhibit distinct melting points and X-ray powder diffraction (“XRPD”) patterns with well-defined peaks. (DTX-101 (Byrn 1994) at 1.) Crystalline solids are often used as active ingredients in pharmaceutical products.

Polymorphs exist when the drug substance crystallizes in different crystal packing arrangements, all of which have the same elemental composition—in other words, the same compound can be packed in different crystal arrangements. (DTX-102 (Byrn 1995) at 4.) Different polymorphic forms will typically have the same effect on disease in the body, but can have different chemical and physical properties, including melting point, apparent solubility, dissolution rate, optical properties, vapor pressure, density, and XRPD patterns, among others. (DTX-196 (Yu) at 1-6; DTX-103 (Byrn 1999) at 95.) The polymorphic forms can also exhibit different particle shape and different mechanical properties including hardness, flowability, and compactability. (JTX-145 (FDA Guideline) at 35.)

“Systematic investigation of a compound to determine whether it is prone to polymorphism, as well as the nature of the polymorphism [], is routine practice in pharmaceutical pre-formulation studies.” (JTX-224 (Caira) at 3; *see also* DTX-97 (Borka 1990) at 1.) Further, it was well known in the prior art that different polymorphs of a compound can be made by simple techniques, of which the most common is dissolving the substance in a limited amount of a heated solvent and then cooling the resulting solution. (DTX-158 (Pavia) at 7; DTX-102 (Byrn 1995) at 4.) This well-established toolbox of techniques can be applied to conduct a “polymorph screen” in which the crystallization of a given substance is undertaken using a range of conditions and common solvents to identify the possible polymorphic forms of the compound. (DTX-125 (Guillory) at 7.)

Differentiating among the various solid forms of a substance is “generally a routine matter.” (DTX-101 (Byrn 1994) at 1.) By 2002, there were numerous, well-known analytical techniques for studying and characterizing polymorphs. (*See generally* DTX-196 (Yu).) One of the analytical techniques used and taught in the prior art is X-ray powder diffraction (“XRPD”). (*See generally id.*; JTX-224 (Caira) at 18-36.)

#### **D. The Prior Art Taught the Use of PDE4 Inhibitors to Treat Psoriasis**

The '536 patent, while primarily about the enantiomer, contains a claim limitation directed to the use of apremilast to treat psoriasis. Psoriasis is a chronic skin condition that affects about 1% to 3% of the total U.S. population. (*See* DTX-215 (Peters 2000) at 1; DTX-217 (Greaves 1995) at 1; JTX-67 (Dyke 1999) at 12.) Although not usually life-threatening, psoriasis is a disabling disease that can cause significant morbidity, and currently has no cure. (*See* DTX-215 (Peters) at 1; DTX-217 (Greaves) at 1; JTX-67 (Dyke 1999) at 12.) The most common form of psoriasis is plaque psoriasis, occurring in about 90% of patients. (DTX-215 (Peters 2000) at 3.) Up to 20% of patients with psoriasis develop psoriatic arthritis, an inflammatory arthritis condition, with symptoms very similar to rheumatoid arthritis. (*Id.* at 4; JTX-67 (Dyke 1999) at 12.)

As of 2002, there were a number of conventional topical and systemic therapies available for the treatment of psoriasis. (DTX-215 (Peters 2000); DTX-217 (Greaves 1995).) However, each of these therapies had its own advantages and disadvantages, and thus a POSA would have been motivated to further develop drugs with different mechanisms of action for treating patients suffering from psoriasis. The prior art taught that PDE4 inhibitors could be therapeutically useful in the treatment of inflammatory conditions and diseases, including psoriasis, by decreasing the production of certain proinflammatory proteins—more specifically, TNF $\alpha$ . (DTX-174 ('358 patent) at 4:35-53; JTX-67 (Dyke 1999) at 12.)

In particular, it was known that excessive or unregulated TNF $\alpha$  production “has been implicated in a number of disease conditions,” including endotoxemia and/or toxic shock syndrome, rheumatoid arthritis, Crohn’s disease, irritable bowel syndrome, cachexia, and Adult Respiratory Distress Syndrome. (DTX-174 (’358 patent) at 1:20-30; *see also* JTX-69 (Muller 1998) at 1 (“Excessive TNF- $\alpha$  levels have been found to be associated with a number of inflammatory and autoimmune conditions including rheumatoid arthritis.”); JTX-66 (Marriott 2001) at 3 (“TNF- $\alpha$  is a key regulator of other pro-inflammatory cytokines and leukocyte adhesion molecules and therefore represents a therapeutic target in a number of conditions where the overproduction of TNF- $\alpha$  is associated with a pathological inflammatory cascade.”).)

As such, the “control of TNF- $\alpha$  levels could be a key to the treatment of a wide range of [inflammatory] diseases,” including psoriasis. (JTX-66 (Marriott 2001) at 3.) One mechanism for inhibiting TNF $\alpha$  production indirectly was by increasing the levels of cAMP in inflammatory leukocytes. cAMP is a second messenger that mediates “biological responses to a variety of hormones, neurotransmitters, autocoids and drugs.” (JTX-67 (Dyke 1999) at 1.) cAMP levels, in turn, are primarily controlled by PDEs which break down and inactivate cAMP. (DTX-174 (’358 patent) at 4:12-14.) The prior art thus disclosed that PDE4 inhibition “is particularly effective in . . . the inhibition of inflammatory mediator release,” including the release of TNF $\alpha$  cytokines. (*Id.* at 4:17-19.)

These observations led to the “potential use of PDE4 inhibitors as anti-inflammatory agents for the treatment of asthma and other inflammatory disorders [] receiv[ing] considerable attention from the pharmaceutical industry.” (JTX-67 (Dyke 1999) at 1.) Indeed, Celgene told the world in its ’358 patent that decreasing “TNF $\alpha$  levels, increasing cAMP levels, and inhibiting PDE IV thus constitute valuable therapeutic strategies for the treatment of many inflammatory, infectious,

immunological or malignant diseases,” including psoriasis. (DTX-174 ('358 patent) at 4:35-42.) Early clinical studies “suggest[ed] the therapeutic potential of [PDE4 inhibitor] compounds in the treatment of psoriasis.” (JTX-67 (Dyke 1999) at 12.)

**E. The Prior Art Taught That Thalidomide Analogues Are Potent PDE4 Inhibitors**

Thalidomide is an immunomodulatory drug that “has been shown to be clinically useful in a number of conditions including various immunological disorders and cancers,” such as rheumatoid arthritis. (JTX-66 (Marriott 2001) at 1, 4.) Its clinical activity *in vivo* “is attributed to the wide ranging immunological and non-immunological properties possessed by this drug,” including anti-TNF $\alpha$  activity. (*Id.* at 1.) As such, the prior art taught that “it would seem likely that novel compounds designed using thalidomide[']s structure as a lead would allow optimisation of its immunological and anticancer properties while decreasing its side effects.” (*Id.* at 4.)

This investigation led to the “synthesis of analogues with greatly enhanced immunological activity and with similar decreased toxicity,” including drugs with potent PDE4 inhibitory activity. (JTX-66 (Marriott 2001) at 1; JTX-69 (Muller 1998) at 5.) By 2002, a number of different thalidomide analogues were characterized in the laboratory, and were being assessed in clinical studies for safety and efficacy in inflammatory diseases. (JTX-66 (Marriott 2001) at 6.) These initial studies were “encouraging” and provided an “exciting prospect” for the potential clinical efficacy of thalidomide analogues in a wide range of conditions that could be ameliorated by PDE4 (and thus TNF $\alpha$ ) inhibition, such as psoriasis. (*Id.* at 7.)

**F. Clinical Studies of Apremilast for the Treatment of Psoriasis**

In 2000, apremilast was specifically disclosed in the '358 patent in its racemic form as a compound having selective PDE4 inhibitory activity. (DTX-174 ('358 patent) at 4:35-42, 14:34-55 (Example 12).) By 2014, there was a continued interest in further developing “improved, orally

available therapies,” such as apremilast, for the treatment of psoriasis “that limit disease progression without impacting on patient life-style and well-being.” (JTX-226 (Palfreeman) at 1.) For example, in 2012, the clinical efficacy and safety of apremilast were investigated in a phase IIb randomized, dose-ranging study, where patients with moderate to severe psoriasis were administered oral apremilast 10 mg twice daily, 20 mg twice daily, and 30 mg twice daily. (DTX-153 (Papp 2012) at 1.) The “[d]oses were titrated in the first week to mitigate potential dose-dependent adverse events of apremilast; all patients reached the target dose by day 5.” (*Id.* at 2.) The results from the phase IIb study showed “apremilast 30 mg had the most favourable outcome,” and thus this dose was chosen for further investigation in patients with moderate to severe psoriasis in phase III trials. (*Id.* at 7.) In addition, “the rate of overall reported adverse events was generally related to dose”—headache and diarrhea were reported more frequently with apremilast 30 mg than in the other groups. (*Id.* at 5, 7.)

### III. CLAIM CONSTRUCTION

The parties agreed to, and the court adopted, the following definitions of the following claim terms:

Claim Term(s)	Agreed-to Constructions
“stereomerically pure” ’638 patent ’536 patent ’541 patent	“a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound”
“stereomerically pure [(+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisoindoline-1,3-dione/compound]” ’638 patent ’536 patent	“a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound, wherein that one stereoisomer is (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisoindoline-1,3-dione”

Claim Term(s)	Agreed-to Constructions
'541 patent	
"enantiomerically pure" <sup>2</sup>	"a stereomerically pure composition of a compound having one chiral center"
'101 patent	
'243 patent	

#### IV. ARGUMENT

##### A. The '638 Patent

The asserted claims of the '638 patent are directed to a pharmaceutical composition suitable for oral administration comprising from about 10 mg to about 200 mg of stereomerically pure apremilast and a pharmaceutically acceptable carrier, excipient, or diluent. Each and every one of the asserted claim limitations is disclosed in the prior art '358 patent, and therefore the asserted claims are anticipated. The asserted claims are also obvious based on either the combination of the '358 patent with WO '606, which teaches that the compounds of the same Formula I are "preferably administered as a substantially chirally pure isomer," or the combination of the '358 patent with Takeuchi, which teaches synthesis and stereomeric purity of a nonracemizable analogue of thalidomide, as well as pharmacological testing of the same. (DTX-159 (WO '606) at 12; DTX-168 (Takeuchi).) The asserted claims are further obvious based on obviousness-type double patenting over claim 31 of U.S. Patent No. 8,093,283 (JTX-6 ("the '283 patent")).

##### i. The Asserted Claims of the '638 Patent

Asserted claims 3 and 6, and the claims from which they depend, read:

1. A pharmaceutical composition comprising stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisoindoline-1,3-dione, or a pharmaceutically acceptable salt,

<sup>2</sup> "[E]nantiomerically pure" also appears in claim 1 of the '173 patent and claim 1 of the '283 patent.

solvate or hydrate, thereof; and a pharmaceutically acceptable carrier, excipient or diluent.

2. The pharmaceutical composition of claim 1 wherein said pharmaceutical composition is suitable for parenteral, transdermal, mucosal, nasal, buccal, sublingual, or oral administration to a patient.
3. The pharmaceutical composition of claim 2 wherein said pharmaceutical composition is suitable for oral administration to a patient.
4. The pharmaceutical composition of claim 2 wherein the amount of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminisoindoline-1,3-dione is from 1 mg to 1000 mg.
5. The pharmaceutical composition of claim 4 wherein the amount of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminisoindoline-1,3-dione is from 5 mg to 500 mg.
6. The pharmaceutical composition of claim 5 wherein the amount of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminisoindoline-1,3-dione is from 10 mg to 200 mg.

(JTX-3 ('638 patent) at 31:26-32:12.)

Because the Asserted Claims are dependent claims, they incorporate all of the limitations of the claims from which they depend. 35 U.S.C. § 112(d). *See also Alcon Rsch. LTD v. Apotex, Inc.*, 687 F.3d 1362, 1367 (Fed. Cir. 2012) (“[B]ecause a dependent claim narrows the claim from which it depends, it must ‘incorporate . . . all the limitations of the claim to which it refers.’”)

## **ii. Prosecution History of the '638 Patent**

Celgene filed the application for the '638 patent in April 2005. This came three years after the filing of its provisional application to which the '638 patent claims priority, and more than six years after the date Amgen contends that the asserted claims were conceived and reduced to practice. Amgen offers no explanation for this delay.

The '638 patent claims were issued after just a single, nonfinal rejection. (JTX-16 ('638 patent FH), 2007-12-03 Non-Final Rejection at 293.) The examiner rejected the pending claims

in the application as being anticipated by the '358 patent, which discloses pharmaceutical compositions comprising apremilast. (*Id.* at 182-83.) Celgene overcame the rejection by arguing that Example 12 in the '358 patent discloses the racemate but not the enantiomer or stereomerically pure enantiomers, and cites to the *Forest* and *Sanofi* cases to argue that the Federal Circuit has ruled that claims to a single enantiomer were not anticipated. (*Id.*, 2008-03-18 Applicant Remarks at 252-54.)

The examiner allowed the claims without further correspondence. (*Id.*, 2008-05-16 Notice of Allowance at 267-69.) A closer look at the *Forest* and *Sanofi* cases reveals why these two cases are factually distinguishable and thus are inapposite. In *Forest*, the Federal Circuit found that a prior art reference was not enabling with respect to the claimed enantiomer. *Forest Labs., Inc. v. Ivax Pharms. Inc.*, 501 F.3d 1263, 1268 (Fed. Cir. 2007). The court found that the prior art reference, a pharmacology paper, did not describe how to obtain the enantiomer. *Id.* In *Sanofi*, the Federal Circuit found that the prior art patent disclosed the racemate and stated that the compounds of the invention included the enantiomers but did not describe how to separate the enantiomers. *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1083 (Fed. Cir. 2008).

Here, the prior art '358 patent explicitly teaches that the compounds of that invention (including the racemic compound containing apremilast) "can be separated into their individual isomers mechanically as by chromatography using a chiral absorbant. Alternatively, the individual isomers can be prepared in chiral form or separated chemically from a mixture by forming salts with a chiral acid" and "so as to obtain either or both substantially free of the other; i.e., in a form having an optical purity of >95%." (DTX-174 ('358 patent) at 8:63-9:12.) Moreover, the '638 patent specification admits that the (+) enantiomer "can be isolated from the racemic compound by techniques known in the art." (JTX-3 ('638 patent) at 9:8-24 (citing references published in

1962, 1972, 1977, and 1981)).

For these reasons, the Court should reject any argument that the *Sanofi* and *Forest* decisions require, or even suggest, that the '638 patent be upheld as valid.

### iii. Priority Date

Amgen has not established, and cannot establish, conception and reduction to practice of the full scope of the asserted claims of the '638 patent before March 20, 2002. Amgen's testimony and documentary evidence do not show that before March 20, 2002, the inventors had a definite and permanent idea of the complete and operative invention, as it is thereafter to be applied in practice, or that there was a physical embodiment with all claim limitations that would work for its intended purpose. *See Cooper v. Goldfarb*, 154 F.3d 1321, 1327-31 (Fed. Cir. 1998) (inventor's laboratory notebook entries showing failure of experiments were sufficient to establish conception but not reduction to practice because the entries did not show testing sufficient to show that the invention was suitable for its intended purpose and there was no corroborated evidence that the successful experiments conducted by another met the claim limitations); *see also Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1170-72 (Fed. Cir. 2006).

Uncorroborated conversations between named inventor Peter Schafer and Amgen's experts regarding Celgene's "ongoing drug discovery program" are insufficient to establish that Celgene conceived and reduced to practice the full scope of the asserted claims of the '638 patent. *See Medichem*, 437 F.3d at 1171-72 ("Even the most credible inventor testimony is *a fortiori* required to be corroborated by independent evidence, which may consist of documentary evidence or testimony of non-inventors."). The asserted claims themselves all require pharmaceutical compositions comprising stereomerically pure apremilast and pharmaceutically acceptable excipients. (JTX-3 ('638 patent) at 31:26-32:12.) Claim 6 further requires from 10 mg to 200 mg of stereomerically pure apremilast. (*Id.* at 32:9-12.) Hearsay about a nonspecific research plan,

such as Celgene's "ongoing drug discovery program," does not equate to a showing that the inventors conceived and reduced to practice the claimed compositions before March 20, 2002.

**iv. Claims 3 and 6 Are Invalid As Anticipated**

Celgene's disclosures in the prior art '358 patent necessarily invalidate claims 3 and 6 of the '638 patent. In first seeking patent protection in Europe for claims directed to stereomerically pure apremilast for the treatment of psoriasis and inflammatory diseases, Celgene relied on teachings identical to those in the '358 patent's specification that identify the racemate and teach separation and purification of the enantiomers. (DTX-106 (EP '148 FH 2009-04-02 correspondence).) Thus, the '358 patent's specification contains disclosures sufficient to anticipate claims 3 and 6 of the '638 patent.

Amgen, as Celgene's successor in interest for the '638 patent, now asks the Court to disregard both the explicit disclosures of the '358 patent and Amgen's predecessor's binding admissions in Europe regarding what is and is not disclosed by the '358 patent to find the '638 patent valid, even though Celgene knew the claims were not novel. Amgen further asks the Court to disregard admissions in the specification of the '638 patent, which provide that apremilast "can be isolated from the racemic compound by techniques known in the art," including HPLC. (*See* JTX-3 ('638 patent) at 9:13-17.) Amgen should not be permitted to escape these binding admissions. *See McCoy v. Heal Sys., LLC*, No. 2020-1484, 2021 WL 1235188, at \*3 (Fed. Cir. Apr. 1, 2021) (the court should accept "the specification's own assertions of what is well known in the art"); *Constant v. Advanced Micro-Devices Inc.*, 848 F.2d 1560, 1570 (Fed. Cir. 1988) ("A statement in a patent that something is in the prior art is binding on the applicant and patentee for determinations of anticipation and obviousness.").

Defendants will prove by clear and convincing evidence that claims 3 and 6 of the '638 patent are invalid as anticipated by the '358 patent. Defendants' expert, Dr. Gordon Gribble, will

explain how a POSA would have found every element of claims 3 and 6 in the prior art '358 patent. First, the '358 patent discloses apremilast in Example 12 and teaches methods for isolating stereomerically pure apremilast. (DTX-174 ('358 patent) at 8:63–9:12 (describing methods to obtain an enantiomer “in a form having an optical purity of >95%”, *i.e.*, >97.5% by weight).) Second, the '358 patent describes pharmaceutical compositions containing compounds, including apremilast, with pharmaceutically acceptable excipients. (*Id.* at 9:22–60 (disclosing oral dosage forms “containing from 1 to 100 mg” of the compound and “at least one pharmaceutically acceptable carrier, diluent, or excipient”).) Third, the '358 patent teaches that those compositions are suitable for oral administration to treat a variety of conditions mediated by PDE4 inhibition. (*Id.* at 4:28–54 (teaching that the disclosed compounds are “particularly” useful in inhibiting PDE4 “and in the treatment of disease states mediated thereby”).) Finally, the compounds of the '358 patent, including apremilast, are taught to be useful in dosages ranging from 1 mg to 100 mg of drug per unit of dosage form. (*Id.* at 9:22–24 (“Oral dosage forms include tablets, capsules, dragees, and similar shaped, compressed pharmaceutical forms containing from 1 to 100 mg of drug per unit dosage.”).)

The explicit disclosures in the '358 patent would have provided a POSA with the entirety of the asserted claimed subject matter. No further analysis need be undertaken. Celgene confirmed this fact when it sought patent protection for claims reciting “optically pure” apremilast in Europe based on the very same disclosures in the '358 patent specification cited above.

Amgen will argue that the '358 patent fails to explicitly call out either apremilast or the other enantiomer of Example 12, stereomerically pure or otherwise. As Dr. Gribble will explain, that suggestion fails to account for the knowledge and experience of a POSA, which would have known that a single enantiomer can be pharmaceutically desirable over the racemate and would

have known how to purify stereoisomers. A POSA reading the '358 patent would immediately envisage stereomerically pure apremilast. See *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (“[A] reference can anticipate a claim even if it does not expressly spell out all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would at once envisage the claimed arrangement or combination.”) (internal quotation and citation omitted). The '358 patent contains unambiguous instructions on how to purify apremilast. (DTX-174 ('358 patent) at 8:63–9:12.) In fact, a POSA would find no vagaries preventing purification of apremilast that could not be solved by someone having undertaken undergraduate training and studies.

Amgen will also argue that the '358 patent is not enabled. Prior art references are presumed to be enabled, and Amgen has not met its burden to show otherwise. See *Proctor & Gamble Co. v. Nabisco Brands, Inc.*, 711 F. Supp. 759, 772 (D. Del. 1989) (finding that P&G failed to meet its burden to show that the prior art was not enabling). As Dr. Gribble will explain, a POSA would have been well versed and equipped to separate the enantiomers of Example 12 to obtain stereomerically pure apremilast without undue experimentation. Further, it is not required that the '358 patent “provide a detailed recipe for preparing” each enantiomer of Example 12 to enable a POSA to prepare the stereomerically pure (+) enantiomer. See *Pfizer Inc. v. Teva Pharmaceuticals USA, Inc.*, 555 Fed. App'x 961, 966-67 (2014) (holding that a patent disclosure enabled compositions of a chemical compound without limitation as to the enantiomeric form or purity where the patent disclosed a method for synthesizing the compound and stated that the compound's “enantiomers may be prepared or isolated by methods already well known in the art”); see also JTX-3 ('638 patent) at 9:8-24 (citing references published in 1962, 1972, 1977, and 1981, admitting that the racemate containing apremilast “is readily prepared using the methods”

disclosed in the '358 patent and that apremilast “can be isolated from the racemic compound by techniques known in the art”).)

Amgen also intends to offer testimony from its European patent law expert, Mr. Christopher Mercer, that Celgene’s admissions regarding the '358 patent should not be considered when weighing anticipation of the '638 patent. Defendants have sought exclusion of Mr. Mercer’s testimony on a number of grounds. Regardless, even if Mr. Mercer does testify, the '638 patent itself provides a party admission that directly contradicts his position. The '638 patent states that stereomerically pure apremilast can be obtained by techniques known in the art, and refers to the '358 patent as an exemplary piece of prior art. (JTX-3 ('638 patent) at 9:13-24.) In other words, while seeking the '638 patent, Celgene confirmed the accuracy of its statements to the European Patent Office. Under the Federal Rules of Civil Procedure, and controlling authority, Amgen cannot disavow the binding admissions of Celgene, the prior assignee of both patents. *See Sherwin-Williams Co. v. PPG Indus., Inc.*, No. CV 17-1023, 2021 WL 211497, at \*2-3 & n.3 (W.D. Pa. Jan. 21, 2021) (Sherwin-Williams bound by the “Valspar admissions” during prosecution where it was “undisputed that Sherwin [was] Valspar’s successor-in-interest”); *see also Proctor & Gamble Co.*, 711 F. Supp. at 770 (“[A] patentee’s representations to the PTO during prosecution of its patent application about the scope of the prior art is a binding admission and should ‘be accepted at face value’ during subsequent litigation over the patents.”)

#### **v. Claims 3 and 6 Are Invalid As Obvious**

Defendants will prove by clear and convincing evidence that claims 3 and 6 of the '638 patent would have been obvious to a POSA over (1) the '358 patent and WO '606 and the knowledge of a POSA and (2) the '358 patent and Takeuchi and the knowledge of a POSA.

Obviousness is a question of law based on an objective analysis of the underlying facts, including (1) the scope and content of the prior art; (2) the differences between the prior art and

the claim at issue; (3) the level of ordinary skill in the pertinent art; and (4) such secondary considerations as commercial success, long-felt but unmet need, and the failure of others. *Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1259 (Fed. Cir. 2012). Obviousness is judged as of the time the invention was made, from the viewpoint of a POSA. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419-20 (2007).

**a. Defendants will establish a *prima facie* case that claims 3 and 6 are invalid as obvious**

**1. Pharmaceutical compositions comprising stereomerically pure apremilast would have been obvious to a POSA based on the '358 patent and WO '606 and the knowledge of a POSA.**

Claims 3 and 6 of the '638 patent would have been obvious based on the teachings of the '358 patent when combined with the teachings of Celgene's WO '606. Like the '358 patent, WO '606 discloses methods for isolating stereomerically pure apremilast, describes pharmaceutical compositions containing compounds of Formula I (including apremilast) with pharmaceutically acceptable excipients, teaches that those compositions are suitable for oral administration to treat a variety of conditions mediated by PDE4 inhibition, and finally that the compounds of Formula I (including apremilast) are useful in dosages ranging from 1 mg to 100 mg of drug per unit of dosage form. (DTX-174 ('358 patent) at 9:22–24; DTX-159 (WO '606) at 24:1–3.) WO '606 further teaches that the compounds of Formula I (including apremilast) “preferably are administered as a substantially chirally pure isomer, (S)- or (R)-.” (DTX-159 (WO '606) at 12:20–22.)

A POSA would be motivated to combine the teachings of the '358 patent and WO '606 because these references discuss the same art (PDE4 inhibitors), disclose the same general family of compounds pharmaceutically active (isoindoline derivatives), and have, on their faces, the same assignee (Celgene). Also, both the '358 patent and WO '606 teach how to separate the disclosed

enantiomers to be stereomerically pure with greater than 95% optical purity. A POSA would have been motivated with a reasonable expectation of success to prepare an oral pharmaceutical composition of stereomerically pure apremilast based on the teachings of the '358 patent and WO '606. Both the '358 patent and WO '606 teach a POSA to purify stereoisomers of PDE4 inhibitors and prepare oral compositions containing these compounds in dosages ranging from 1 mg to 100 mg for use in treating a variety of conditions mediated by PDE4 inhibition. A POSA would have been motivated with a reasonable expectation of success to separate and purify the enantiomers of the racemic mixture containing apremilast using chiral column chromatography, including to an optical purity of 99%. A POSA would have known that chiral column chromatography, chiral acid separation, and asymmetric synthesis can yield a single isomer of a compound having greater than 99% optical purity, and a POSA would have reasonably expected that such routine methods would result in stereomerically pure apremilast.

A POSA also would have been motivated with a reasonable expectation of success to isolate the individual isomers of the compound of Example 12 in the '358 patent and WO '606 and study the pharmacological activity of each isomer compared to each other and to the racemate. A POSA would have known that one isomer can be pharmaceutically or biologically active, and the other isomer can result in adverse effects or toxicity (or have no activity), and a POSA would have preferred a stereomerically pure compound over the racemate as a pharmaceutical agent.

Of particular relevance to this case is chiral chromatography, a process wherein a column of support particles or beads separates the two enantiomers of a racemate, which is dissolved in a solution. In the 1990's, chiral columns were widely commercially available with a limited number of appropriate solutions to achieve separation of enantiomers. A POSA would have been well practiced in chiral chromatography, which they would have learned as part of their undergraduate

training.

Another long-known technique is to separate racemates into enantiomers by crystallization with specific salts that generate only one enantiomer or the other. This technique goes back to Louis Pasteur in the 19th century. Apremilast, however, would have been recognized by a POSA as a poor candidate for this salt method because it is a neutral molecule and does not form salts.

Finally, a POSA would have been practiced in making stereomerically pure compounds by asymmetric synthesis, which primarily yields only one enantiomer. Asymmetric synthesis uses a purified enantiomer as a starting material or catalyst to drive the final product in the direction of one enantiomer. Here, several of the starting materials for Example 12 of the '358 patent could be converted into pure enantiomers to carry out asymmetric synthesis to arrive at stereomerically pure apremilast.

Amgen will argue that the '638 patent cannot be obvious, because a POSA would never have read the '358 patent or selected the compound of Example 12 for further pharmaceutical development. Such selection arguments fall under the Federal Circuit's "lead compound test" for obviousness of a novel pharmaceutical compound—*i.e.*, a compound that was never previously disclosed in the literature. That test looks to the prior art to design a new compound by chemically modifying a "lead compound" in the prior art. Here, apremilast is not new—it was explicitly and inherently disclosed in the '358 patent. The experts agree that no chemical modification to the compound of Example 12 is needed to obtain apremilast. When a compound has been previously disclosed, the Federal Circuit dictates that the lead compound test no longer applies and, instead, general obviousness analysis governs. *See generally Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007). Moreover, a POSA would have had reason to believe that a stereomerically pure isomer of the compound of Example 12 would have the desirable

property of PDE4 inhibition. Under general obviousness analysis, the Court only must weigh whether the prior art would have led to the claimed subject matter using the flexible approaches set forth by the Supreme Court in *KSR*. See *Aventis Pharma*, 499 F.3d at 1301 (“Requiring an explicit teaching to purify the 5(S) stereoisomer from a mixture in which it is an active ingredient is precisely the sort of rigid application of the TSM [teaching, suggestion, motivation] test that was criticized in *KSR*.”); see also *In re Adamson*, 275 F.2d 952, 954–55 (C.C.P.A. 1960) (holding that an isolated stereoisomer is obvious over the prior art disclosure of the racemate given insufficient showing of any unexpected result, explaining that following the prior art teachings is doing “no more than the obvious” where the prior art suggests to a POSA that the racemates disclosed in a reference may be resolved into their individual enantiomers).

Amgen leans heavily on its irrelevant lead-compound analysis, defending against obviousness by emphasizing that the '358 patent contains no pharmacological or clinical data, as well as noting that none of the compounds disclosed therein was commercially available when the '638 patent was prosecuted. Those arguments are a distraction. Properly applying a general obviousness analysis, a POSA need not be motivated to select one compound, or even one enantiomer, over another from the '358 patent. *Novartis Pharm. Corp. v. West-Ward Pharms. Int'l Ltd.*, 923 F.3d 1051, 1060 (Fed. Cir. 2019) (finding that the District Court erred in requiring clear and convincing evidence that a POSA would *select* the lead compound and that the proper test is whether a POSA would have been motivated to *modify* the prior art) (emphasis added). Rather, a POSA would take as true all of the '358 patent's teachings, including the specifically disclosed utility of treating diseases mediated by PDE4 inhibition. Moreover, a POSA would have been drawn to the compounds named in the '358 patent's Examples, which they would have understood to be compounds of particular interest to the patentee, a large pharmaceutical company. Based on

the combined teachings of the '358 patent and WO '606, a POSA would have desired to separate and purify the enantiomers of Example 12 (and other Examples) before moving on to formulation of compositions and clinical testing.

**2. Pharmaceutical compositions comprising stereomerically pure apremilast would have been obvious to a POSA based on the '358 patent and Takeuchi and the knowledge of a POSA.**

A POSA would have combined the disclosures of the '358 patent regarding isolating stereomerically pure apremilast with Takeuchi because Takeuchi teaches how to separate two enantiomers of a chemically related compound to apremilast. The reason to combine prior art teachings need not be explicit and may come from any source. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361-62 (Fed. Cir. 2007); *SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1356 (Fed. Cir. 2000). Takeuchi contains a detailed teaching of the exact materials and process that could be used to purify enantiomers to more than 99% optical purity. (DTX-168 (Takeuchi) at 2.) Takeuchi further discloses obtaining optical resolution of racemic compound 3 by HPLC with chiral column—specifically, “Diacel Chiralcel AD” and “eluting with ethanol.” (*Id.*) A POSA applying the teachings of the '358 patent in combination with Takeuchi would have reasonably expected to obtain the enantiomers of Example 12 with 99% optical purity.

**3. Amgen's rebuttal arguments are not persuasive.**

Amgen's rebuttal to *prima facie* obviousness weighs heavily on two concepts: selection of a lead compound and a reasonable expectation of success. Neither concept finds support in the facts or law.

The Federal Circuit has authoritatively dismissed any requirement that a claim to a purified enantiomer from a disclosed racemate requires analysis under the special “lead compound test.” *Compare Aventis Pharma*, 499 F.3d at 1301, with *UCB, Inc. v. Accord Healthcare, Inc.*, 890 F.3d

1313, 1328-29 (Fed. Cir. 2018). In such situations, the patent challenger need only identify a *reason* to purify the enantiomers. Unlike *UCB*, where the district court found that there were reasons not to pursue the racemate, let alone further purify the enantiomers, this case squarely follows *Aventis*, where a potential drug was exemplified in the prior art and which also taught purification of the enantiomers. Amgen errs when it suggests that some additional motivation to select the racemate of Example 12, or even the specific enantiomers, is required to find the claims obvious.

In fact, as Dr. Gribble will explain, even if the Court applies the lead compound test, the '358 patent discloses a small number of exemplary racemates of Formula I. A POSA reading the '358 patent would understand that the Examples represent an intentional choice by the patentee to illustrate compounds of particular interest for pharmaceutical development. As such, a POSA would begin with the Examples (and not the general Formula I) to obtain pure enantiomers based on at least the general understanding in the art that single enantiomers can be preferential to racemates as therapeutic compounds, as well as the specific teachings in WO '606. (DTX-159 (WO '606) at 12:20–22.) In other words, the '358 patent discloses a limited and finite number of compounds that a POSA would understand are useful as PDE4 inhibitors.

Amgen's argument against a reasonable expectation of success fares no better. As Dr. Gribble will explain, the separation and purification of enantiomers is both routine and predictable. That is especially so when the prior art teaches certain methods for separation in order to achieve substantially pure enantiomers, as in this case. The '358 patent (and WO '606) explicitly teaches that apremilast, as an enantiomer of Example 12, can be obtained with an optical purity of greater than 95%. By definition, a POSA would have had a reasonable expectation of success in the endeavor.

Amgen's position really boils down to generalized arguments about unpredictability in the pharmaceutical arts and lack of enablement of the prior art. Whether the end product of pharmaceutical development results in an FDA-approved drug matters not to patentability. See *Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1331 (Fed. Cir. 2017) ("The fact that Gilenya was the first to receive FDA approval for commercial marketing does not overcome the fact that solid multiple sclerosis compositions were already known. Thus, we agree with the Board that Novartis' proffered evidence is not probative of the nonobviousness inquiry."). A pharmaceutical composition can be obvious regardless of whether it is ever approved for marketing. And, of course, the Federal Circuit has held that analyzing whether a prior art reference is enabling of the claimed subject matter has no place in an obviousness analysis. See *Raytheon Techs. Corp. v. Gen. Elec. Co.*, 993 F.3d 1374, 1380 (Fed. Cir. 2021) ("While a reference must enable someone to practice the invention in order to anticipate under § 102(b), a non-enabling reference may qualify as prior art for the purpose of determining obviousness under § 103.") (citing *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1578 (Fed. Cir. 1991)); *Beckman Instruments Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989) ("Even if a reference discloses an inoperative device, it is prior art for all that it teaches.").

**b. Amgen's evidence in support of purported objective indicia does not overcome the *prima facie* obviousness.**

Amgen's experts raise a variety of purported objective indicia of nonobviousness with respect to the '638 patent, none of which, alone or in combination, casts doubt on or overcomes the obviousness of the '638 patent.

**1. Skepticism**

Amgen has not offered any evidence demonstrating skepticism in the industry of stereomerically pure apremilast. Before arguing skepticism, Amgen must present a nexus between

the objective evidence and the purportedly novel elements of the claim. *See Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1327 (Fed. Cir. 2008) (skepticism lacked the requisite nexus to the claimed invention when the evidence of skepticism did not result from what is novel in the claim). Here, the racemate, which necessarily contains apremilast, was known. (DTX-174 ('358 patent) at 14:34-55.) Thus, any skepticism must be directed to making apremilast stereomerically pure. Amgen has never even addressed this issue.

Instead of establishing the proper nexus, Amgen has argued that a POSA would have been skeptical about the safety of apremilast because of known issues with a different compound, thalidomide. While thalidomide and apremilast share some structural aspects, Celgene itself repeatedly distinguished apremilast and similar compounds from thalidomide, noting their improved safety profile arising from the many structural differences. Amgen may be disappointed in its predecessor's admissions, but it cannot rewrite history. As far as the industry would have been concerned, apremilast would have reasonably been expected to be a suitable drug candidate.

## 2. Unexpected Results

Amgen fails to apply the proper legal standard—that results are only unexpected when they differ in kind rather than degree from what is known in the closest prior art. *In re Merck*, 800 F.2d 1091, 1098-99 (Fed. Cir. 1986). Amgen does, however, concede that the closest prior art compound is the racemate of Example 12, which necessarily includes apremilast. Amgen's hair-splitting complaint is that the prior art fails to include pharmacological data for Example 12, and Amgen thus argues that it may be excused from comparing stereomerically pure apremilast to the racemate—*i.e.*, applying the proper legal standard. Amgen can identify no legal authority that permits substituting other compounds for the closest prior art simply because a document (the '358 patent) does not disclose some details (specifically, pharmacological data) or because the closest prior art compound was not commercially available. *Trustees of Columbia Univ. v. Illumina, Inc.*,

620 F. App'x 916, 932 (Fed. Cir. 2015) (“[T]here is no requirement that the closest prior art be commercialized.”) (citing *In re Merchant*, 575 F.2d 865, 869 (C.C.P.A. 1978)).

Even when Amgen addresses what it considers to be relevant properties of the racemate and other PDE4 inhibitors, Amgen forgets that a difference in degree is not sufficient to establish an unexpected result. For example, Amgen argues that apremilast has an unexpectedly better therapeutic index and tolerability than the racemate and other PDE4 inhibitors, including cilomilast and roflumilast. But a difference in therapeutic index as a PDE4 inhibitor, or the severity of adverse events, represents a classic case of a difference in degree, not kind. Amgen is not arguing that it was unexpected that apremilast is a PDE4 inhibitor, or that stereomerically pure apremilast has some other pharmaceutical property that the prior art compounds do not.

The prior art is replete with examples of oral PDE4 inhibitors for the treatment of inflammatory conditions, including psoriasis, and immunological diseases, such as arthritic conditions. (See DTX-174 ('358 patent); JTX-67 (Dyke 1999); JTX-69 (Muller 1998); JTX-68 (Muller 1999).) That one of the enantiomers of Example 12 would be suitable for an oral pharmaceutical composition was expected based on the prior art. (See DTX-174 ('358 patent) at 17:44-19:55 (Examples 21-25).) Amgen's arguments highlighting topical and injectable medications for psoriasis and psoriatic arthritis do not render unexpected oral treatment of these diseases, which patients have preferred and received for years through methotrexate, anti-inflammatories, and steroids.

### 3. Failure of Others

Once again, Amgen appears to misinterpret what is required to establish objective indicia. Here, the claims are directed to pharmaceutical compositions of stereomerically pure apremilast, so any failure of others would have to be a failure of others to purify and formulate apremilast. Yet Amgen argues that the failure of other PDE4 inhibitors to obtain FDA approval establishes a

failure of others. This argument fails for two reasons. First, FDA approval is a distinct issue from the patentability of a composition. *See Novartis*, 853 F.3d at 1331. Second, Defendants' expert Dr. Clive Page will explain that the decision to develop, or even seek FDA approval for, these other PDE4 inhibitors involved complex, business-driven considerations that overshadowed, and may not even have been related to, the scientific findings associated with each product. In fact, Dr. Page is personally aware of several PDE4-inhibitor products that were abandoned even though the products showed promising clinical results and may have been approvable. Dr. Page will also explain that before apremilast, FDA already had approved an oral PDE4 inhibitor—roflumilast—for the treatment of an inflammatory condition. This testimony will directly counter any argument that others failed to develop oral PDE4 inhibitors.

#### **4. Long-Felt, Unmet Need**

Amgen's purported long-felt, but unmet need again fails to have a nexus to the claimed subject matter. Neither does Amgen bother to address whether there was a long-felt, unmet need for stereomerically pure apremilast, or pharmaceutical compositions thereof.

Rather, without citation to any prior art, Amgen invents a so-called "need" for a safe and effective PDE4 inhibitor suitable for human use in a pharmaceutical composition. That "need," however, had already been met by roflumilast and other prior art compounds. To the extent that Amgen is arguing that there was a long-felt, but unmet need for Otezla<sup>®</sup>, that argument ignores Otezla<sup>®</sup>'s role in the marketplace. The clinical experts agree that other medications, including those available before Otezla<sup>®</sup>, are as, or even more, effective in treating psoriasis and psoriatic arthritis. Amgen cannot dispute that these medications were already fulfilling the need for a safe, effective treatment for these conditions. In fact, Otezla<sup>®</sup> falls in the middle of the spectrum with respect to safety and efficacy among the various oral, topical, and injectable options for treating psoriasis and psoriatic arthritis.

Amgen's only evidence of a long-felt need is confidential testing of apremilast related to its therapeutic index, of which a POSA could not have been aware—rendering it irrelevant to any purported long-felt but unmet need. *See In re Gershon*, 372 F.2d 535, 538 (C.C.P.A. 1967) (if others have not become aware that a need exists, then it is clear that this need cannot be deemed to be one that is long-felt). Moreover, As Dr. Page will explain, therapeutic index data may be collected and interpreted in many different ways, yielding many different results based on who is analyzing the data and what adverse events are being observed. Such subjective testing and interpretation unrelated to the claimed subject matter should not impact the Court's finding on obviousness.

## 5. Commercial Success

Amgen cannot establish that there is a nexus between any purported evidence of commercial success and the asserted claims of the '638 patent. In arguing otherwise, Amgen conveniently ignores the existence of the '358 patent, which was a "blocking" patent and served as an economic disincentive to others developing and/or commercializing apremilast, thereby "discount[ing] the weight of [any] evidence of commercial success." *Acorda Therapeutics*, 903 F.3d at 1339.

Indeed, the '358 patent, which discloses and claims apremilast (as discussed above) was listed in the Orange Book in connection with Otezla® prior to its expiration. (DTX-384 at 1000 (Approved Drug Products with Therapeutic Equivalence (35th ed.)).) Such evidence only further confirms that the manufacture, marketing, and commercial use of a product containing apremilast in the United States would infringe at least claim 1 of the '358 patent. In other words, it would not be feasible to practice the asserted claims of the '638 patent without practicing the claims of the '358 patent. As such, Defendants' expert Mr. Hoffman will testify that at the time of the relevant priority date of the '638 patent, the '358 patent would have disincentivized other

companies from developing and commercializing a product falling within the scope of the asserted claims of the '638 patent, without risking infringement of the '358 patent until its expiration on October 30, 2018.

Putting aside the blocking patent, the evidence will further show that the marketplace performance of Otezla® is attributable to other factors unrelated to the allegedly novel features of the '638 patent, and thus lacks a nexus to the claimed invention for this additional reason. *First*, to the extent Otezla® has an allegedly distinct mechanism of action compared to other therapies available as of the relevant priority date, such features are attributable only to the active pharmaceutical ingredient apremilast, which was known and disclosed in the prior art '358 patent. Amgen thus cannot “establish a nexus between the evidence and the *claimed invention*,” which is a “fundamental requirement that must be met before secondary considerations can carry the day.” *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (emphasis added).

*Second*, expert testimony will show that Celgene and Amgen employed various extensive marketing efforts—including, but not limited to, direct-to-consumer advertising, sales representatives detailing to physicians, and the provision of product samples to patients—that influenced prescribing behavior and directly contributed to sales of Otezla®. *Prometheus Labs., Inc. v. Roxane Labs., Inc.*, 805 F.3d 1092, 1101 (Fed. Cir. 2015) (affirming district court’s finding of no nexus where the alleged “growth in revenue” was due to patentee’s “actions in marketing, increasing the price [], and introducing a series of rebates to stimulate sales of the drug, rather than from the treatment of method claimed in the” asserted patent). In arguing for commercial success, Amgen has also failed to take into account pricing incentives that have driven the marketplace performance of Otezla®, such as rebates and discounts to third-party payers and copay programs and services for patients.

*Third*, Amgen has failed to isolate or apportion any purported “success” among the Asserted Claims of the Patents-in-Suit, let alone to the other patents that have been or are currently listed in the Orange Book in connection with Otezla® that are not currently being asserted against Defendants, including the prior art ’358 patent. As Mr. Hoffman will testify, it is improper for Amgen to attribute the entire value of the marketplace performance of Otezla® to the asserted claims of the ’638 patent without isolating any value to any individual claim and without appropriately addressing the prior art and other Orange Book-listed patents.

**vi. Claims 3 and 6 Are Invalid under the Obviousness-Type Double Patenting Doctrine.**

Celgene’s patent prosecution strategy has resulted in an unlawful extension of Amgen’s monopoly. Amgen’s patents run afoul of the axiom that a patentee may not claim the same invention in different patents with different expiration dates. *See Gilead Scis., Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208, 1212 (Fed. Cir. 2014) (“It is self-evident that on the expiration of a patent the monopoly created by it ceases to exist, and the right to make the thing formerly covered by the patent becomes public property. It is upon this condition that the patent is granted.”) (quoting *Singer Mfg. Co. v. June Mfg. Co.*, 163 U.S. 169, 185 (1896)). Here, Celgene’s decision to prosecute the ’283 patent and others related to the ’638 patent as “continuation-in-part” applications should have required any claim in the ’638 patent claiming the same subject matter as claims in related patents to expire on the same date as the earliest expiring patent in the family—*i.e.*, the expiration date of the ’283 patent.

The ’638 patent issued out of a patent-prosecution morass of continuation applications, divisional applications, and continuation-in-part applications. An individual seeking a patent on more than one invention may file a continuation application, which permits patenting of additional claims from the same application while maintaining the earliest priority date of the invention. An

individual may also file divisional applications, usually based on a request of the Patent Office, to split subject matter from a common specification to avoid the Patent Office's rule that different categories of patent claims cannot be included in the same set of issued patent claims. A continuation-in-part application is a special type of continuation application where the individual wants to maintain the earliest priority date but adds new material to the specification. *See* MPEP § 211.05 ("A continuation-in-part application may include matter not disclosed in the prior-filed application," noting, however, that "[o]nly the claims of the continuation-in-part application that are disclosed in the manner provided by 35 U.S.C. 112(a) in the prior-filed application are entitled to the benefit of the filing date of the prior-filed application."). The Patent Office uniquely treats continuation-in-part applications by assigning two priority dates to a single application. For all matter contained in the original specification, the individual retains the right to rely on the earliest priority date to defend against a patent challenge. *Id.* Any new matter added to the specification is awarded the priority date on which the matter was added. *Id.* In other words, claims in the continuation-in-part application that rely on the newly added information are treated like a separate patent that was independently filed on the later priority date.

A patent granted from a continuation-in-part application expires twenty years from the date of the earliest priority date, regardless of the new information added, just as a continuation or divisional application does. *See* MPEP § 2701 ("A patent granted on a continuation, divisional, or continuation-in-part application that was filed on or after June 8, 1995, will have a term which ends twenty years from the filing date of earliest application for which a [priority] benefit is claimed."). This quirk can result in a patent being granted on a later-filed continuation-in-part application that expires earlier than other related patents based on the original application, including a continuation or divisional application, because of various term adjustments and

extensions. The Federal Circuit has uniformly held that such a circumstance can render the extended or adjusted patent invalid for illegally extending the monopoly when the later-expiring claimed subject matter is the same as, or an obvious variant of, a claimed subject matter in the earlier-expiring patent. *See, e.g., Abbvie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1373 (Fed. Cir. 2014) (explaining that a “crucial purpose” of the obviousness-type double-patenting doctrine is “to prevent an inventor from securing a second, later expiring patent for the same invention,” which can occur when “[p]atents claiming overlapping subject matter that were filed at the same time still can have different patent terms due to examination delays at the PTO”).

Here, the application that became the '283 patent was originally filed as a continuation-in-part application stemming from the same priority application as the '638 patent. In fact, claim 31 of the '283 patent contains both added matter (a crystalline form of apremilast) and old matter (an oral-pharmaceutical composition of enantiomerically/stereomerically pure apremilast). Thus, claim 31 represents a species within the larger genus of claims 3 and 6 of the '638 patent, only differing by specifying the crystalline form of apremilast (Form A) in the pharmaceutical composition. This difference between claim 31 of the '283 patent and claims 3 and 6 of the '638 patent does not render claims 3 and 6 patentably distinct from claim 31. A chemist would not have had to modify the compound claimed in claim 31 to obtain the compound claimed in claims 3 and 6. Yet claim 31 of the '283 patent expires on March 19, 2023, and claims 3 and 6 of the '638 patent expire on February 16, 2028.

How did this happen? Due to a delay by the Patent Office, Celgene obtained a patent term adjustment for the claims of the '638 patent, thereby extending the monopoly from March 19, 2023 to November 1, 2024. Then, Celgene obtained a patent term extension for the '638 patent as

permitted under the Hatch-Waxman Act based on Otezla®'s approval, thereby further extending the monopoly to February 16, 2028.

Recently, the Federal Circuit held that patent term extensions under the Hatch-Waxman Act may be challenged only under some circumstances, none of which has been raised by Defendants in this case. *See Novartis AG v. Ezra Ventures LLC*, 909 F.3d 1367, 1375 (Fed. Cir. 2018). Patent term adjustments, however, are not afforded such protection. *Abbvie*, 764 F.3d at 1373. Thus, Amgen may be permitted to extend the patent life under the Hatch-Waxman Act but should not benefit from the additional monopoly created by the patent term adjustment. By invalidating the patent term adjustment, the expiration date of the '638 patent should be reduced by 609 days, which equates to the number of days afforded in the patent term adjustment.

Under the principle of obviousness-type double patenting, claims 3 and 6 of the '638 are obvious in view of claim 31 of the '283 patent. Based on claim 31 of the '283 patent, a POSA would have been motivated with a reasonable expectation of success to prepare a pharmaceutical composition comprising stereomerically pure apremilast, and a pharmaceutically acceptable carrier, excipient or diluent, for oral administration in the form of a single unit dosage form, including a capsule or tablet, with 10 mg to 200 mg of stereomerically pure apremilast.

#### **B. The '536 Patent**

The sole asserted claim of the '536 patent claims a method of treating psoriasis by orally administering to a patient about 10 mg to about 200 mg per day of stereomerically pure apremilast in a tablet or capsule as either a single or a divided dose, wherein the stereomerically pure compound "comprises greater than 97% by weight of (+) isomer based on the total weight percent of the compound." (JTX-7 (the '536 patent) at 30:63-31:3, 31:14-16.) Each and every one of these limitations is disclosed in the prior art '358 patent, and therefore the asserted claim is anticipated. Defendants will also present clear and convincing evidence that the asserted claim

would have been obvious to a POSA as of the priority date.

The question of obviousness comes down to “whether a person of ordinary skill in the art would have been motivated to combine those teachings to derive the claimed subject matter with a reasonable expectation of success.” *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1375 (Fed. Cir. 2013). Years before the ’536 patent was filed, it was well-established that PDE4 inhibitors could be therapeutically useful in the treatment of psoriasis due their ability to prevent the overproduction of TNF $\alpha$ , an inflammatory protein that was known to be implicated in the pathology of various inflammatory diseases. (DTX-174 (’358 patent) at 4:35-54; JTX-67 (Dyke 1999) at 12.) The prior art further taught that thalidomide and thalidomide analogues (such as apremilast) potently inhibit PDE4 activity and, consequently, TNF $\alpha$  production, and therefore had potential for treating a wide range of inflammatory conditions. (JTX-66 (Marriott 2001) at 3-4; JTX-69 (Muller 1998) at 5.) Although thalidomide can cause birth defects, it was known and understood that this teratogenicity is only associated with one particular isomer of the drug. As such, pharmaceutical companies, including Celgene, were continuing to develop compounds “designed using thalidomide[']s structure as a lead [, which] would allow optimization of its immunological and anticancer properties while decreasing its side effects.” (JTX-66 (Marriott 2001) at 4.) The prior art disclosed stereomerically pure apremilast, a thalidomide analogue, for inhibiting PDE4 and TNF $\alpha$  production. (DTX-174 (’358 patent) at 7:1-3.) In particular, Celgene’s ’358 patent taught that the racemate of apremilast, provided in Example 12, could be prepared as a stereomerically pure compound comprising greater than 97% of the (+) isomer using routine techniques in the prior art. (*Id.* at 8:63-9:12.)

Amgen has no credible response to the collective teachings in the prior art. It claims that a POSA would not have been motivated to pursue apremilast because of the known teratogenic

effects of thalidomide. However, Amgen points to *nothing* in the *prior art* teaching away from or discouraging the use of thalidomide analogues to inhibit PDE4 and treat inflammatory conditions. Nor do Amgen's purported secondary considerations support nonobviousness, especially given the earlier, blocking '358 patent, which rebuts assertions of commercial success, unmet need, and praise. *See Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1339 (Fed. Cir. 2018).

Alternatively, to the extent the asserted claim of the '536 patent is found not obvious, then it is invalid under § 112 because the specification does not describe any clinical data supporting or enabling the claimed method of treating psoriasis.

**i. The Asserted Claim of the '536 Patent**

Asserted claim 6 of the '536 patent, and the claim from which it depends, reads:

1. A method of treating psoriasis, which comprises orally administering to a patient having psoriasis about 10 mg to about 200 mg per day of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminobenzimidazole-1,3-dione, wherein the compound is administered in the form of a tablet or capsule as either a single or divided dose.
6. The method of claim 1, wherein the stereomerically pure compound comprises greater than about 97% by weight of (+) isomer based on the total weight percent of the compound.

(JTX-7 ('536 patent) at 30:63-31:16 (claims 1, 6).)

**ii. The Asserted Claim of the '536 Patent Is Not Entitled to a Priority Date Earlier Than March 20, 2002**

The '536 patent claims priority to U.S. Provisional Application No. 60/366,515, filed on March 20, 2002. (*Id.* at 1.) However, Amgen claims that it is entitled to an earlier priority date of December 14, 2001, for assessing obviousness because that is when the inventors supposedly conceived of the claimed method of treatment. But the only evidence put forth by Amgen shows, at most, that the alleged inventors were in possession of animal data showing that apremilast was relatively nontoxic. There is no evidence that the inventors conceived of the full scope of "a

method of treating psoriasis” in a patient, as required by claim 6 of the ’536 patent, or that the inventors were diligent in reducing the purported invention to practice. *See Sing v. Brake*, 222 F.3d 1362, 1367 (Fed. Cir. 2000) (“A conception must encompass all limitations of the claimed invention.”); *Coleman v. Dines*, 754 F.2d 353, 359 (Fed. Cir. 1985) (“It is settled that in establishing conception a party must show possession of every feature recited in the count, and that every limitation of the count must have been known to the inventor at the time of the alleged conception.”).

**iii. The Asserted Claim of the ’536 Patent Is Anticipated by the ’358 Patent.**

Even accepting Amgen’s alleged priority date, clear and convincing evidence will show that the claimed method of treatment would have been anticipated as of December 2001 (or March 2002) over the ’358 patent.

For the same reasons discussed above with respect to the asserted claims of the ’638 patent, the ’358 patent discloses “stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisoindoline-1,3-dione,” *i.e.*, apremilast, comprising “greater than about 97% by weight of (+) isomer,” as required by asserted claim 6 of the ’536 patent.

The ’358 patent further discloses that its compounds can be used to inhibit PDE4 and TNF $\alpha$  production, for the treatment of certain inflammatory conditions. (DTX-174 (’358 patent) at 1:5–11; *id.* at 4:28–31.) More specifically, the ’358 patent discloses that “[d]ecreasing TNF $\alpha$  levels, increasing cAMP levels, and inhibiting PDE IV thus constitute valuable therapeutic strategies for the treatment of many inflammatory, infectious, immunological or malignant diseases,” including psoriasis and rheumatoid arthritis. (*Id.* at 4:35–54; *see also id.* at 22:29–35 (claims 17–18).)

The ’358 patent teaches dosage forms and dose amounts for the compounds disclosed therein, including apremilast, that are therapeutically effective for treating psoriasis. In particular,

the '358 patent provides that its compounds “can be administered orally, rectally, or parenterally, alone or in combination with other therapeutic agents including antibiotics, steroids, etc., to a mammal in need of treatment.” (*Id.* at 7:3-7.) The '358 patent further discloses oral dosage forms, including tablets and capsules containing from 1 mg to 100 mg of drug per unit dosage. (*Id.* at 9:22-24.) The compositions can “be administered in a single or multiple dosage regimen to human subjects and other mammals.” (*Id.* at 9:53-60.) Accordingly, based on the disclosures in the '358 patent, a POSA would have readily understood that an oral dosage form containing from 1 mg to 100 mg of stereomerically pure apremilast would be therapeutically effective for treating psoriasis, which considerably overlaps with the dosage range in claim 6 of the '536 patent (10-200 mg).

As such, Defendants' experts will testify that a POSA reading the '358 patent would be able to immediately envisage a method of treating psoriasis by administering 10-200 mg of stereomerically pure apremilast (comprising greater than 97% by weight of the (+) isomer), in the form of a tablet or capsule, and in either a single dose or a divided dose, and that claim 6 is anticipated.

**iv. The Asserted Claim of the '536 Patent Would Have Been Obvious**

If not anticipated, the evidence will clearly and convincingly show that asserted claim 6 of the '536 patent would also have been obvious to a POSA in view of (1) the '358 patent and WO '606 in view of Dyke 1999 and Marriott 2001 and the knowledge of a POSA; (2) the '358 patent and Takeuchi in view of Dyke 1999 and Marriott 2001 and the knowledge of a POSA; and (3) the '358 patent in view of Dyke 1999, Marriott 2001, and Muller 1998 and the knowledge of a POSA.

- a. The prior art disclosed stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisindoline-1,3-dione that comprises greater than about 97% by weight of (+) isomer.**

As discussed above with respect to the '638 patent, the '358 patent in combination with WO '606 and the knowledge of a POSA and/or the '358 patent in combination with Takeuchi and the knowledge of a POSA renders obvious the limitations requiring "stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisindoline-1,3-dione" comprising "greater than about 97% by weight of (+) isomer," as recited in asserted claim 6 of the '536 patent. In fact, while the '358 patent explicitly discloses separation of enantiomers to greater than 95% optical purity, a POSA would have understood from all of these prior art references and their own experience that enantiomers can be routinely and successfully separated to optical purities greater than 99%.

A POSA developing a chiral pharmaceutical product would have been motivated to make it as optically pure as possible, including with an optical purity of 100%. It would have simply been a matter of routine experimentation for a POSA to do so with apremilast as of the relevant priority date. Expert testimony will show that at that time, a POSA would have known that chiral column chromatography, chiral acid separation, and asymmetric synthesis could yield a single isomer of a compound having greater than 97% optical purity.

- b. It would have been obvious to administer a PDE4 inhibitor like apremilast to treat patients with psoriasis.**

As of 2002, a POSA would have understood that psoriasis has no cure, and thus the goal of treatment is to decrease the severity and extent of clinical symptoms. Thus, a POSA would have been motivated to further develop an effective systemic drug therapy with a different mechanism of action for treating psoriasis and with a tolerable safety profile.

As discussed, it was known in the prior art that increased levels of TNF $\alpha$  are involved in the pathogenesis of inflammatory skin conditions, such as psoriasis, and thus a POSA would have been further motivated to target this pathway in finding an alternative treatment for such diseases. Indeed, the '358 patent teaches that "[e]xcessive or unregulated TNF $\alpha$  production [] has been implicated in a number of disease conditions," including "endotoxemia and/or toxic shock syndrome, rheumatoid arthritis, Crohn's disease, IBD [inflammatory bowel disease], cachexia and Adult Respiratory Distress Syndrome." (DTX-174 ('358 patent) at 1:20-30.) The '358 patent discloses that one method of blocking TNF $\alpha$  production is by elevating the levels of cAMP produced by inflammatory cells. The '358 patent further provides that this can be achieved by inhibiting the PDE4, which is "particularly effective in both the inhibition of inflammatory mediator release and the relaxation of airway smooth muscle." (*Id.* at 4:16-20.)

According to the '358 patent, its compounds, including apremilast, are useful in inhibiting PDE4, and are thus "valuable therapeutic strategies for the treatment of many inflammatory, infectious, immunological or malignant diseases," such as psoriasis and rheumatoid arthritis. (*Id.* at 4:35-54; *see also id.* at 22:29-35 (Claims 17-18).) Other prior art available as of 2001 confirms the '358 patent's teachings regarding the use of PDE4 inhibitors to treat inflammation. For example, Dyke 1999 discloses that preclinical and clinical studies investigating the efficacy of PDE4 inhibitors "suggest[] the therapeutic potential of such compounds in the treatment of psoriasis." (JTX-67 (Dyke 1999) at 12.)

In light of the teachings of the '358 patent and Dyke 1999 regarding the therapeutic potential of PDE4 inhibition for treating inflammatory diseases like psoriasis, a POSA would have further looked to Marriott 2001 and Muller 1998, both of which confirm that thalidomide analogues were known to be potent PDE4 inhibitors. Marriott 2001 provides that thalidomide has

been shown to inhibit TNF $\alpha$ , which “represents a therapeutic target in a number of conditions where the overproduction of TNF $\alpha$  is associated with a pathological inflammatory cascade.” (JTX-66 (Marriott 2001) at 3.) Despite reports associating thalidomide with birth defects, Marriott 2001 nevertheless suggests that “it would seem likely that novel compounds designed using thalidomide structure as a lead would allow optimization of its immunological and anticancer properties while decreasing its side effects.” (*Id.* at 2, 4.) This investigation led to the synthesis of thalidomide analogues with “greatly enhanced immunological activity and with similarly decreased toxicity,” including those that potently and selectively inhibit PDE4. (*Id.* at 2, 4.) As early as November 1999, Celgene had at least two PDE4 inhibitors under clinical development for the treatment of inflammatory conditions. (*Id.* at 6.) Because “laboratory studies and initial clinical studies [were] encouraging,” Marriott 2001 ultimately concludes that “[b]earing in mind the potential clinical efficacy of thalidomide in a wide range of conditions with very little therapeutic option, it is an exciting prospect that these novel compounds may provide us with a new generation of clinically effective drugs.” (*Id.* at 7.)

Muller 1998 is consistent with the teachings of Marriott 2001. In that study, the authors, including a named inventor of the '536 patent, prepared numerous thalidomide analogues with the goal of “increas[ing] the TNF- $\alpha$  inhibitory potency of thalidomide and eliminat[ing]/decreas[ing] its teratogenic potency.” (JTX-69 (Muller 1998) at 1.) Muller 1998 explained that “these thalidomide analogs are potent inhibitors of PDE4” and that they can “control TNF $\alpha$  levels by inhibition of PDE4.” (*Id.* at 5.) The results showed that for the majority of analogues, there was a “good correlation between TNF- $\alpha$  inhibition and PDE4 inhibition” and that the compounds “appear to inhibit TNF- $\alpha$  by elevation of cellular cAMP levels.” (*Id.* at 4.)

For at least these reasons, in light of the teachings of the '358 patent, in view of Dyke 1999, Marriott 2001, and Muller 1998, a POSA would have been motivated to further develop thalidomide analogues such as apremilast with PDE4-inhibitory activity to treat psoriasis, with a reasonable expectation of success. A POSA would have been motivated to combine the '358 patent with Dyke 1999, Marriott 2001, and Muller 1998, given that each of these references relates to PDE4 inhibiting compounds and the use of such compounds to treat similar inflammatory conditions, including psoriasis.

Despite what Amgen may argue, that thalidomide was known to be associated with certain adverse effects would not have discouraged a POSA from pursuing thalidomide analogues as a potential treatment for psoriasis. "A reference teaches away when it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought" by the patentee. *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (quotations omitted). To the contrary, the prior art—Marriott 2001—expressly concludes that thalidomide analogues provide an "exciting prospect" for a "new generation of clinically effective drugs." (JTX-66 (Marriott 2001) at 7.) Moreover, if thalidomide analogues were as dangerous as Amgen suggests, there would have been no reason for pharmaceutical companies like Celgene to continue developing thalidomide analogues for therapeutic use. And yet the evidence will show that Celgene was actively involved in this space well before 2001. Indeed, Celgene went so far as to file a patent application covering thalidomide analogues, including apremilast, telling the public it was because of their usefulness in inhibiting PDE4 and treating psoriasis. *In re Young*, 927 F.2d 588, 591 (Fed. Cir. 1991) ("Patents are part of the literature of the art and are relevant for all they contain."). A POSA thus would have had the reasonable expectation that apremilast could work to treat psoriasis, and there is no evidence indicating otherwise.

**c. It would have been obvious to administer 10–200 mg of apremilast per day.**

As discussed above, the '358 patent disclosed therapeutically effective doses of apremilast ranging from 1 mg to 100 mg per day in the form of a tablet or capsule, which significantly overlaps with the claimed dosage range of 10 mg to 200 mg per day. *See infra* Section IV.A.iv. Where, as here, “there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence that: (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations.” *Galderma*, 737 F.3d at 738. Amgen cannot carry this burden. Amgen notably does not allege that any prior art taught away from the claimed range, or that the claimed range is supported by any unexpected results or other objective indicia. Thus, doses within the claimed range would have been obvious over the '358 patent.

**d. There are no secondary considerations of nonobviousness.**

Where “a claimed invention represents no more than the predictable use of prior art elements according to established functions . . . evidence of secondary indicia are frequently deemed inadequate to establish non-obviousness.” *Ohio Willow Wood Co. v. Alps S., LLC*, 735 F.3d 1333, 1344 (Fed. Cir. 2013). That is certainly the case here. Moreover, Amgen’s alleged evidence of secondary considerations “actually results from something *other* than what is both claimed and *novel* in the [asserted] claim [of the '536 patent], [so] there is no nexus to the merits of the claimed invention.” *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1385 (Fed. Cir. 2015).

*No skepticism, failure of others, unexpected results, or long-felt need.* As discussed above with respect to the '638 patent, there is no evidence of skepticism, failure of others,

unexpected results, or long-felt need for a safe and effective PDE4 inhibitor suitable for human use in a pharmaceutical composition that supports the nonobviousness of the asserted claim of the '536 patent.

*No long-felt need.* Amgen will contend that Otezla<sup>®</sup> satisfied a long-felt, unmet need for a safer treatment for moderate plaque psoriasis that does not present the same potential barriers to adherence of other treatment options. Amgen's alleged evidence of long-felt need is not sufficient to overcome the *prima facie* obviousness of the asserted claim of the '536 patent.

*First*, the asserted claim does not require that the claimed method of treatment is a "safer" treatment for moderate plaque psoriasis, or that it "does not present the same potential barriers to adherence of other treatment options." Nor are any of these characteristics described in the specification of the '536 patent as being the allegedly novel aspect of the claimed invention over the prior art. Thus, Amgen's alleged evidence regarding long-felt but unmet need for a treatment for plaque psoriasis (in addition to Behçet's disease and psoriatic arthritis) has no relation to, and is not commensurate in scope with, the invention claimed in the asserted claim of the '536 patent.

*Second*, Otezla<sup>®</sup> did not satisfy any long-felt need in the treatment of patients suffering from psoriasis that was not met by other existing therapies. Even before Otezla<sup>®</sup> was approved by FDA, there were a number of existing therapies that were effective and used for treating psoriasis. For example, methotrexate was known to be an effective therapy for patients with psoriasis and "has been the standard of care in the clinical setting for over 50 years." (JTX-118 at 2.) Even today, methotrexate "remains the most commonly used treatment for psoriasis." (*Id.*) The evidence will show that dermatologists in fact prescribe methotrexate more often than Otezla<sup>®</sup>. While methotrexate can be associated with serious side effects, that has not deterred many patients from initiating and continuing methotrexate therapy to this day.

Another class of drugs that were available and effective for systemically treating psoriasis before Otezla® was biologic drugs, which had “transformed the standard of care for patients,” particularly those with severe disease. (DTX-372 (Reid) at 8.) By the time Otezla® was approved in 2014, there were a number of biologic therapies that had been approved by FDA for the treatment of psoriasis. The benefit of using biologics is that they are designed to “target specific components of the immune system that are involved in psoriasis pathogenesis.” (*Id.* at 4.) Thus, biologic drugs are more effective in treating psoriasis than conventional therapies and are associated with fewer side effects as well.

Even after Otezla® became commercially available, there was a continued interest in further developing biologic drugs as more information became known about the etiology of psoriasis. (*Id.* at 6.) Studies show that with these newer biologic drugs, “[f]or the first time, significant numbers of patients are achieving PASI90 or PASI100 with treatment”—*i.e.*, complete clearance of their skin. (*Id.*) Thus, to the extent there was any alleged long-felt need for the treatment of psoriasis before Otezla®, it was met by the use of conventional, oral systemic therapies, such as methotrexate, and first-/second-generation biologic drugs. To the extent that such need still existed after Otezla®, it was met by the new generation of biologic drugs, which have shown the ability to achieve 100% clearance of psoriatic plaques and lesions.

Contrary to Amgen’s assertions, because biologic treatments provide vastly superior efficacy and faster onset of relief, the evidence will show that issues like needle phobia or potential side effects did not deter many patients from pursuing treatment with a biologic drug before (or even after) Otezla®’s approval. Even for the small subset of patients who did have needle phobia, traditional, oral therapies were (and still are) always an option.

*Third*, Otezla® did not satisfy any alleged unmet need. There is currently no cure for psoriasis, and thus the goal of any treatment is to decrease the severity and extent of clinical symptoms. While Otezla® has been shown to reduce the severity of psoriasis in clinical trials, it provides only a modest benefit in clearance of plaques and lesions, and is not more effective than conventional oral therapies, such as methotrexate. (DTX-367 (Armstrong) at 1; *see also* DTX-377 (Wittmann) at 1.) Thus, Otezla® does not offer any particular advantages in terms of the ability to alleviate a patient's clinical symptoms.

Otezla® is also much less effective than biologics, including those that predated Otezla®, in clearing psoriatic lesions. As discussed, biologic drugs can completely clear a patient's psoriatic lesions from head to toe, something that was not possible with conventional therapies and is not possible with Otezla®. While Amgen will argue that Otezla® has a safety profile that is more favorable than any other available therapy, the evidence will show otherwise. Defendants' experts will testify that while Otezla® is generally well tolerated in psoriasis patients, it can also be associated with significant gastrointestinal-related side effects, such as diarrhea, cramping, and nausea. (JTX-107 (Otezla® Label).)

Thus, it was well known that the dose should be titrated to mitigate the severity and risk of these side effects (as taught in the prior art). And even with a titrated dose, Defendants' experts will testify that about 40–50% of patients decide that they do not want to move forward with Otezla® and discontinue treatment because they still cannot tolerate the gastrointestinal-related side effects. (*See, e.g.*, DTX-348 (Zerilli) at 5 (“Nevertheless, the twice-daily dosing might not be advisable if nonadherence is a concern, and the gastrointestinal side effects may be troublesome.”); DTX-376 (Rendon) at 13 (“The potential side effects of . . . apremilast are usually not life-threatening, but might be sufficient to warrant discontinuation.”).)

*Fourth*, to the extent there are any advantages associated with Otezla<sup>®</sup>, they result from the compound itself, which Celgene disclosed in the '358 patent. Amgen thus cannot “establish a nexus between the evidence and the *claimed invention*” — a “fundamental requirement that must be met before secondary considerations can carry the day.” *In re Huai-Hung Kao*, 639 F.3d at 1068. At best, Amgen’s objective evidence “results from something other than what is both claimed and novel in the claim, [so] there is no nexus to the merits of the claimed invention.” *Id.* In any event, as discussed above with respect to the '638 patent, the '358 patent acted as a “blocking patent” that prevented others from marketing apremilast— “discount[ing] the weight of [any] evidence of commercial success, failure of others, and long-felt but unmet need”—as well as any purported praise. *Acorda Therapeutics*, 903 F.3d at 1339.

***No clinical success.*** There is no evidence that Otezla<sup>®</sup> has attained substantial success in the clinic as a widely prescribed treatment for plaque psoriasis or moderate plaque psoriasis. First, Amgen’s alleged evidence of “substantial success” has no nexus to, and is not commensurate with, the scope of the asserted claim of the '536 patent. In particular, the asserted claim does not narrow the type of disease to be treated to “moderate plaque psoriasis” but rather broadly claims the treatment of psoriasis. Nor does the specification of the '536 patent describe the treatment of moderate plaque psoriasis as being the allegedly novel aspect of the claimed invention over the prior art.

In addition, as discussed above, the evidence will show that many physicians prescribe methotrexate to patients with moderate to severe psoriasis more often than Otezla<sup>®</sup> because methotrexate has similar efficacy, it is available as a generic (and therefore is less expensive), and patients are attracted to the fact that methotrexate is dosed only once weekly (as opposed to twice a day for Otezla<sup>®</sup>). (*See DTX-377 (Wittmann)* at 10 (“However, it is difficult to see physicians

making major changes to their prescribing habits given the current lack of clear cut evidence for superiority of apremilast and the concerns about the initial gastrointestinal tolerability issues.”.) Moreover, because Otezla® is associated with significant gastrointestinal-related side effects, a significant number of patients have difficulty tolerating Otezla® and decide to discontinue treatment for this reason. As such, Otezla® has not achieved substantial success in the clinic, particularly when compared against other available treatment options.

Despite what Amgen may argue, Amgen’s and Celgene’s marketing efforts for Otezla® would have influenced physicians to prescribe Otezla® over other treatments. Physicians often receive free samples (starter packs) from branded drug suppliers, including Otezla®. Numerous studies have been published demonstrating the effect of pharmaceutical-sample availability on prescribing behavior. (*See, e.g.*, DTX-477 (Warrier); DTX-478 (Symm); DTX-479 (Chew).)

**No praise.** Amgen’s anecdotal evidence from dermatologists and rheumatologists does not demonstrate widespread industry praise for Otezla®. *Bayer*, 713 F.3d at 1377 (holding that “bare journal citations and self-referential commendation fall well short of demonstrating true industry phrase”). Moreover, as discussed above, Otezla® does not have any improved efficacy over traditional, oral systemic therapies such as methotrexate, or biologic therapies. In fact, a number of patients (up to 50%) discontinue treatment even after taking the drug on a titration schedule. That Celgene received the Thomas Alva Edison Patent Award is not probative of widespread industry praise for Otezla®, given the complete lack of information as to what factors or judgments were taken into consideration in deciding who would receive this award. *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1342 (Fed. Cir. 2020) (finding that patentee failed to establish a nexus between evidence of alleged praise, the selection of a presentation at the American Chemical Society’s National Meeting, and the claimed method “because there was no evidence that the

presentation was selected due to the claimed method”). Even to the extent there is any praise regarding the use of Otezla<sup>®</sup>, it is only attributable to the active ingredient, apremilast, which was already disclosed in the prior art ’358 patent. *In re Huai-Hung Kao*, 639 F.3d at 1068.

*No commercial success.* There is no evidence of commercial success sufficient to overcome the obviousness of the asserted claim of the ’536 patent, for the same reasons discussed above with respect to the ’638 patent.

**v. The Asserted Claim of the ’536 Patent Lacks Adequate Written Description**

To satisfy the written description requirement, “the patent specification must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.” *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479 (Fed. Cir. 1998) (internal quotations and citations omitted). This means that “the disclosure must . . . convey with reasonable clarity to those skilled in the art that . . . [the inventor] was in possession of the invention.” *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000) (citation omitted).

To the extent the asserted claim of the ’536 patent is found not obvious because the prior art fails to disclose clinical data teaching the efficacy of apremilast in treating psoriasis, the specification of the ’536 patent itself fails to satisfy the written description requirement. The specification of the ’536 patent does not provide any clinical data supporting the use of apremilast to treat psoriasis. Rather, the only data that are provided are in Example 8, which describes an *in vivo* study in an LPS-induced lung neutrophilia ferret model. However, this model relies on bacterial activation of an immune response to predict the activity of a drug *in vivo* in an animal model. Thus, to the extent the asserted claim is not obvious, such a disclosure in the specification is not representative of the full scope of the Asserted Claims requiring methods of treating psoriasis

in a human patient, and is not sufficient to show that the named inventors had possession of the claimed method of treating psoriasis as of the filing date.

**vi. The Asserted Claim of the '536 Patent Is Not Adequately Enabled**

To satisfy enablement, “the specification of a patent much teach those skilled in the art how to make and use the full scope of the claimed invention without ‘undue experimentation.’” *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 940 (Fed. Cir. 2010) (quoting *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F. 3d 1361, 1365 (Fed. Cir. 1997)); *see also Nat’l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1195-96 (Fed. Cir. 1999); *In re Goodman*, 11 F.3d 1046, 1050 (Fed. Cir. 1993); 35 U.S.C. § 112 ¶ 1. “Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations,” including the quantity of experimentation necessary and the amount of direction or guidance presented. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

Similar to written description, to the extent the asserted claim of the '536 patent is found not obvious, then the specification of the '536 patent fails to enable the full scope of the claims, and a consideration of the *Wand* factors indicates that undue experimentation would be required. To the extent clinical data are required to show the effectiveness of a PDE4 inhibitor in treating psoriasis, a POSA would have to conduct undue experimentation to arrive at the claimed method.

**C. The '101 Patent**

Asserted claims 1 and 15 of the '101 patent are directed to crystalline Form B of enantiomerically pure apremilast, comprising four XRPD peaks, and a solid pharmaceutical composition comprising that crystalline Form B of enantiomerically pure apremilast.

Amgen has not carried, and cannot carry, its burden to show that the asserted claims of the '101 patent are entitled to a priority date earlier than March 27, 2008, the filing date of the application that issued as the '101 patent. *See PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d

1299, 1305-06 (Fed. Cir. 2008) (holding that the patent owner has burden to come forward with evidence to prove entitlement to claim priority to earlier filing date). Amgen relies on Example 2 in the '515 application, filed on March 20, 2002, to argue the asserted claims are entitled to the earlier filing date. Nothing in Example 2, however, shows that the named inventors of the '101 patent were in possession of the claimed crystalline apremilast Form B. *See id.* at 1306 ("It is elementary patent law that a patent application is entitled to the benefit of the filing date of an earlier filed application only if the disclosure of the earlier application provides support for the claims of the later application, as required by 35 U.S.C. § 112.") (internal citation omitted). Thus, the '052 Publication and the '049 Publication, each published on October 2, 2003, qualify as prior art to the '101 patent. Clear and convincing evidence at trial will show that these two prior art publications render the asserted claims of the '101 patent obvious. Amgen does not present any argument in response to Defendants' *prima facie* obviousness of the asserted claims as of March 27, 2008, other than repeating its unsupported argument that the asserted claims are entitled to an earlier priority date.

Clear and convincing evidence at trial will also show that the asserted claims of the '101 patent would have been obvious as of March 20, 2002, in view of the '358 patent and the knowledge of a POSA. As described above for the '638 and '536 patents, the '358 patent teaches the pharmaceutical utility of the disclosed compounds, including apremilast, which would have motivated a POSA to prepare and formulate enantiomerically pure apremilast for use in a pharmaceutical composition as a PDE4 inhibitor. Preparation and identification of polymorphs was routine in the prior art for pharmaceutical and formulation research, and therefore, a POSA would have performed routine experimentation to prepare solid forms of apremilast for formulation, and would have obtained enantiomerically pure crystalline Form B apremilast.

Defendants will show that additional prior art related to polymorph screening in the pharmaceutical industry published before March 20, 2002, further supports the obviousness of the asserted claims of the '101 patent.

Amgen's rebuttal arguments fail. Amgen rehashes several arguments it makes with respect to the '638 patent, discussed above. Amgen's other rebuttal arguments are lack of motivation to investigate crystalline forms of apremilast and a reasonable expectation of success. Both arguments fail. Defendants will show at trial a wealth of prior art that would have motivated a POSA to prepare and identify polymorphs of enantiomerically pure apremilast as a routine practice in the prior art for pharmaceutical and formulation research. Amgen relies heavily on a general concept of unpredictability in polymorphism. The mere fact that results of a polymorphic screening are not entirely predictable in advance, and must be confirmed through routine testing, does not mean that any obtained crystalline form is nonobvious. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success").

Amgen has not asserted any objective indicia of nonobviousness with respect to the claimed crystalline apremilast Form B. Thus, objective indicia of nonobviousness have no effect on the obviousness of the claimed crystalline apremilast Form B. *See Horizon Medicines LLC v. Alkem Labs Ltd.*, No. CV 18-1014-RGA, 2020 WL 7022591, at \*3 (D. Del. Nov. 30, 2020).

Another basis of invalidity of the '101 patent is obviousness-type double patenting, which "is designed to prevent an inventor from securing a second, later expiring patent for the same invention." *Abbvie*, 764 F.3d at 1373. Obviousness-type double patenting can exist in a few contexts, including when "[p]atents claiming overlapping subject matter that were filed at the same time still can have different patent terms due to examination delays at the PTO." *Id.* (citing 35

U.S.C. § 154(b) (patent term adjustments)); *see also Magna Electronics, Inc. v. TRW Automotive Holdings Corp.*, Nos. 1:12-cv-654, 1:13-cv-324, 2015 WL 11430786, at \*4-5 (W.D. Mich. Dec. 10, 2015) (following *Abbvie*, finding that a patent can act as double-patenting reference against another patent in the same family (*i.e.*, with the same priority date) where the patent at issue was set to expire after the reference patent because of patent term adjustment).

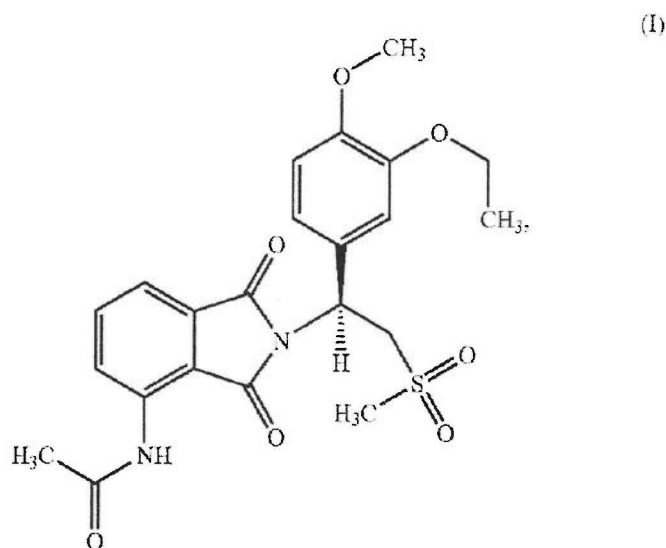
Here, U.S. Patent No. 9,433,606 (“the ’606 patent,” JTX-220) and U.S. Patent No. 9,018,243 (“the ’243 patent,” JTX-10) are double-patenting references against the ’101 patent. The Federal Circuit decision in *Novartis* does not change this conclusion. In *Novartis*, the Federal Circuit determined “that obviousness-type double patenting does not invalidate a validly obtained [Patent Term Extension]” where it is the “earlier-filed, earlier-issued [patent], not the later-filed, later-issued [patent], that has the later expiration date, due to a statutorily-allowed term extension under § 156.” *Novartis*, 909 F.3d at 1373, 1374. Here, Defendants have challenged the ’101 patent’s patent term adjustment (PTA)—not a PTE granted under Section 156. *Novartis* is inapplicable because of statutory and policy differences between the PTA and the PTE. *See Merck & Co. v. Hi-Tech Pharmacal Co.*, 482 F.3d 1317, 1322-24 (Fed. Cir. 2007).

Amgen has not argued that claims 1 and 15 of the ’101 patent are not obvious in view of claim 1 of the ’243 patent or claim 1 of the ’606 patent. Thus, the Asserted Claims of the ’101 patent are invalid under the obviousness-type double-patenting doctrine.

**i. The Asserted Claims of the ’101 Patent**

Asserted claims 1 and 15 of the ’101 patent read:

1. A Form B crystal form of the compound of Formula (I):



which is enantiomerically pure, and which has an X-ray powder diffraction pattern comprising peaks at about 10.1, 13.5, 20.7, and 26.9 degrees 2 $\theta$ .

15. A solid pharmaceutical composition comprising the crystal form of any one of claims 1 and 2 to 13.

(JTX-5 ('101 patent) at claims 1, 15.)

Thus, claim 1 of the '101 patent is directed to the crystalline Form B of enantiomerically pure apremilast, comprising four XRPD peaks. Claim 15 is directed to a solid pharmaceutical composition comprising the crystalline Form B of enantiomerically pure apremilast. According to the Court's adopted construction, "enantiomerically pure," as it appears in the Asserted Claims of the '101 patent, means "a stereomerically pure composition of a compound having one chiral center." See Claim Construction Order (D.I. 187) at 2. Because apremilast has one chiral center, "enantiomerically pure" means "stereomerically pure," as it appears in the asserted claims of the '638 patent and the '536 patent.

Consistent with the common practice and knowledge in the prior art, the '101 patent states that a "solid form screening study" was performed for apremilast ("Compound A") in which "Forms A, B, C, D, E, F, G and an amorphous form" "were prepared." (JTX-5 ('101 patent) at

52:57-60.) The '101 patents further states that “solution evaporation studies” and “cooling crystallization studies” were performed with solvents commonly used for polymorph screening studies including “acetone, acetonitrile, methylene chloride and tetrahydrofuran.” (*Id.* at 51:1-6, 15-20.)

**ii. The Asserted Claims of the '101 Patent Are Not Entitled to a Priority Date Earlier Than March 27, 2008**

Amgen has failed to carry its burden to show that the asserted claims of '101 patent are entitled to a priority date of March 20, 2002. *See PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1305-06 (Fed. Cir. 2008) (holding that the patent owner has burden to come forward with evidence to prove entitlement to claim priority to earlier filing date). The '101 patent, a continuation in part, is not entitled to a priority date earlier than March 27, 2008, because the patent applications to which the '101 patent claims priority do not provide sufficient written description to support the full scope of the asserted claims of the '101 patent. *See id.* at 1306 (“It is elementary patent law that a patent application is entitled to the benefit of the filing date of an earlier filed application only if the disclosure of the earlier application provides support for the claims of the later application, as required by 35 U.S.C. § 112.”) (internal citation omitted)

Amgen relies on Example 2 in the '515 application to argue that the asserted claims are entitled to the '515 application's filing date. In Example 2 in the '515 application, a solid of an enantiomerically pure apremilast was synthesized and purified. (JTX-43 ('515 application) at 28-30.) Amgen cannot show that Example 2 in the '515 application contains a description to show that the inventors had performed routine prior art experimentation and made a crystalline form of enantiomerically pure apremilast, let alone crystalline apremilast Form B. Therefore, the description in the '515 application does not demonstrate to a POSA that the inventors had possession of crystalline Form B of enantiomerically pure apremilast recited in the asserted claims

of the '101 patent.

The '515 application does not convey to a POSA that the named inventors invented crystalline apremilast Form B by the '515 applications' filing date. The written description requirement limits patent protection to those who actually "conceive of the complete and final invention with all its claimed limitations and disclose the fruits of that effort to the public." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1353 (Fed. Cir. 2010). It is well settled that "[o]ne shows that one is 'in possession' of the invention by describing the invention, with all its claimed limitations." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). Thus, it is insufficient as written description, for purposes of establishing priority of invention, to provide a specification that does not unambiguously describe all limitations of the claimed invention. *Hyatt v. Boone*, 146 F.3d 1348, 1354 (Fed. Cir. 1998). Nothing in the '515 application shows that the inventors had conceived, or were in possession, of the asserted claims of the '101 patent, including all of the claimed limitations, by March 20, 2002.

Example 2 in the '515 application is titled "synthesis of Compound A." (JTX-43 ('515 application) at 28.) A POSA would understand that Example 2 provides a recipe to chemically synthesize Compound A (*see id.* at 28-30), which is defined in the '515 application as "an enantiomerically pure form of (+)-2-[1-(3-Ethoxy-4-Methoxyphenyl)-2-Methylsulfonylethyl]-4-Acetylaminoisoindoline-1,3-Dione." (*Id.* at 7.) As provided in Example 2, during the "Preparation of Compound A," "the solvent was evaporated *in vacuo*, and the residue recrystallized from a binary solvent containing ethanol (150 mL) and acetone (75 mL)." (*Id.* at 29.) A POSA would understand this disclosure to describe purifying Compound A after its chemical synthesis from the

precursor. Dr. Hon-Wah Man's deposition testimony<sup>3</sup> confirms this understanding. Dr. Man, who testified he "invent[ed] the apremilast chemical itself," also testified that Example 2 "is the synthesis of apremilast" and that he did not know whether Example 2 results in Form B of apremilast. (See Man Dep. Tr. at 49:6-50:3, 52:10-53:3.) Consistent with Dr. Man's deposition testimony, there is nothing in Example 2, or anywhere else in the '515 application, that could convey to a POSA that the "solid" obtained after this purification step was crystalline, let alone the claimed crystalline apremilast Form B.

As explained below, Example 2 of the '515 application, which is disclosed as Example 2 in the '049 and '052 Publications, renders the Asserted Claims of the '101 patent obvious. Such disclosure, however, does not satisfy the written description requirement. See *Ariad*, 598 F.3d at 1352 ("[A] description that merely renders the invention obvious does not satisfy the requirement."). Thus, "[e]ntitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. It extends only to that which is disclosed." *Lockwood*, 107 F.3d at 1571-72; see also *Los Angeles Biomedical Rsch. Inst. at Harbor-UCLA Med. Ctr. v. Eli Lilly & Co.*, 849 F.3d 1049, 1058 (Fed. Cir. 2017) (affirming PTAB's decision that the claim at issue was not supported by the provisional application, explaining "proof of priority requires written description disclosure in the parent application, not simply information and inferences drawn from uncited references").

Further, the test for written description requires "an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art. Based on that

---

<sup>3</sup> Amgen designated Dr. Man as a corporate representative to testify about various topics, including "[a]ny example, test and/or experiment referenced in the Asserted Patents, and the results obtained from those tests and/or experiments." (See Man Dep. Tr. at 21:20-22:10; see also DTX-430 (Defendants 30(b)(6) Notice of Deposition) at 9 (Topic No. 13).)

inquiry, the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed.” *Ariad*, 598 F.3d at 1351. As the Federal Circuit has repeatedly stated, “actual ‘possession’ or reduction to practice outside of the specification is not enough. Rather, as stated above, it is the specification itself that must demonstrate possession.” *Id.* at 1352; *see also Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1309 (Fed. Cir. 2015) (holding the district court erred by relying on undisclosed clinical protocol to support its written description determination). Therefore, the fact that others were later able to produce crystalline apremilast Form B using well-known prior art processes by following Example 2, as described in Opposition to EP ’483, cannot be used to substitute the written description requirement.

As stated above, the ’101 patent issued from an application filed on March 27, 2008, as a continuation-in-part of an earlier patent application. A continuation-in-part application is a special type of continuation application where the individual wants to maintain the earliest priority date but adds new material to the specification. The Patent Office uniquely treats continuation-in-part applications by assigning two priority dates to a single application. For all matter contained in the original specification, the individual retains the right to rely on the earliest priority date to defend against a patent challenge. Any new matter added to the specification is awarded the priority date on which the matter was added. In other words, claims in the continuation-in-part application that rely on the newly added information are treated like a separate patent that was independently filed on the later priority date. Here, the ’101 patent, which was filed on March 27, 2008, adds new matter regarding preparing and identifying apremilast polymorphs, including crystalline apremilast Form B. (*See* JTX-5 (’101 patent) at 50:49-57:40 (Example 12, titled “Solid Form Screening Studies”), *see also id.* at 5-32 (Figs. 1-28).)

Thus, the asserted claims of the '101 patent, which require the crystalline apremilast Form B, are not entitled to claim priority to the '515 application. Therefore, the earliest priority date to which the asserted claims of the '101 patent are entitled is March 27, 2008.

**iii. The Asserted Claims of the '101 Patent Would Have Been Obvious to a POSA as of March 27, 2008.**

As explained above, the asserted claims of the '101 patent are not entitled to a priority date earlier than March 27, 2008. Patent Publication No. 2003/0187052 ("the '052 Publication") and WO 2003/080049 ("the '049 Publication") were each published on October 2, 2003. Thus, the '052 and the '049 Publications qualify as prior art to the '101 patent.

The evidence at trial will clearly and convincingly show that the asserted claims of the '101 patent are obvious as of March 27, 2008, in view of the '049 Publication and the knowledge of a POSA, as well as in view of the '052 Publication in view of the knowledge of a POSA. For example, the '049 Publication, when read in view of the knowledge of a POSA, renders asserted claims 1 and 15 of the '101 patent obvious. Defendants' expert Dr. Steed will explain that the '049 Publication discloses the synthesis of apremilast ("Compound A") having about 80% to 98% enantiomeric purity. (DTX-189 ('049 Publication) at 28-30 (Example 2); *see also id.* at 6-7, 12-13.) Further, the '049 Publication discloses that enantiomerically pure apremilast "and pharmaceutically acceptable polymorphs, prodrugs, salts, hydrates, clathrates, and solvates thereof" can be incorporated "into pharmaceutical compositions and single unit dosage forms useful in the treatment and prevention of a variety of diseases and disorders." (*Id.* at 9.) The '049 Publication further teaches that the dosage forms can be prepared as "sterile solids (*e.g.*, crystalline or amorphous solids)." (*Id.* at 20.) As Dr. Steed will explain, in view of these teachings that enantiomerically pure apremilast can have different crystalline forms (*i.e.*, exhibit polymorphism), a POSA would have been motivated to perform routine experimentation to prepare different solid

forms with a reasonable expectation to obtain the claimed crystalline apremilast Form B.

The proceedings before the European Patent Office regarding the related EP 2276483 (“EP ’483”) confirm this conclusion. In those proceedings, certain opponents used different but common techniques in the prior art that fell within the conditions described in Example 2, which a POSA would have routinely employed in view of the ’049 Publication, and consistently obtained the claimed crystalline apremilast Form B. (See JTX-225 (EP ’483) at 36-51 (Teva’s Experimental Report); *id.* at 52-63 (Zentiva’s Experimental Report); *id.* at 64-72 (Lek’s Experimental Report).)

The remaining elements of claim 1 directed to four XRPD peaks of the crystalline apremilast Form B do not add any patentable weight, as they are inherent characteristics of the obvious crystalline apremilast Form B. See *Santarus Inc. v. Par Pharmaceutical Cos. Inc.*, 945 F.3d 1184, 1191 (Fed. Cir. 2019) (“inherency may supply a missing claim limitation in an obviousness analysis”); see also *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011) (holding that even though the claimed controlled-release formulation and its associated food effect were not disclosed in the prior art, the formulation would have been obvious and the claimed food effect was an inherent property of the obvious formulation). Therefore, claim 1 of the ’101 patent is obvious in view of the prior art ’049 Publication and the knowledge of a POSA.

The ’049 Publication also renders the additional limitation of claim 15 obvious. Dr. Steed will explain that the ’049 Publication discloses “the incorporation of [apremilast] into pharmaceutical compositions” and that “[p]harmaceutical compositions and single unit dosage forms comprising [apremilast], or a pharmaceutically acceptable polymorph, prodrug, salt, solvate, hydrate, or clathrate thereof, are encompassed by the invention.” (DTX-189 (’049 Publication) at 9; see *id.* at 19.) Therefore, the solid pharmaceutical composition including the crystalline apremilast Form B is obvious in view of the ’049 Publication and the knowledge of a POSA.

The '052 Publication contains identical disclosures to those in the '049 Publication. Therefore, for the same reasons discussed above, the '052 Publication renders obvious the asserted claims of the '101 patent.

Amgen's sole rebuttal argument to Defendants' *prima facie* obviousness of the asserted claims as of March 27, 2008, is that the asserted claims are entitled to an earlier priority date. As explained above, however, Amgen cannot carry its burden to support this assertion.

**iv. The Asserted Claims of the '101 Patent Would Have Been Obvious to a POSA as of March 20, 2002.**

Additionally, the evidence at trial will show clearly and convincingly that asserted claims 1 and 15 of the '101 patent would have been obvious in view of the '358 patent and the knowledge of a POSA. As explained above in Section IV.A.iv, the '358 patent discloses "stereomerically pure" apremilast. Based on the construction of the "enantiomerically pure" element recited in the '101 patent claims as "a stereomerically pure composition of a compound having one chiral center," and for all the same reasons set forth above, the "enantiomerically pure" limitation in the Asserted Claims of the '101 patent is disclosed in the '358 patent.

At trial, Dr. Steed will explain that the crystalline Form B of enantiomerically pure apremilast recited in the asserted claims of the '101 patent is obvious in view of the '358 patent and the common knowledge of a POSA concerning polymorphs. The '358 patent teaches that "[t]he compounds can be administered orally, rectally, or parenterally . . . to a mammal in need of treatment." (DTX-174 ('358 patent) at 7:3-6.) This would have motivated a POSA to formulate enantiomerically pure apremilast. Further, preparation and identification of polymorphs was routine in the prior art for pharmaceutical and formulation research. Therefore, a POSA would have performed routine experimentation to prepare the solid forms of apremilast for formulation, and would have obtained as a result the crystalline Form B of enantiomerically pure apremilast.

The remaining elements of claim 1 directed to four XRPD peaks of the crystalline apremilast Form B do not add any patentable weight, as they are inherent characteristics of the obvious crystalline apremilast Form B. *See Santarus*, 945 F.3d at 1191; *see also In re Kao*, 639 F.3d at 1070. Therefore, claim 1 of the '101 patent is obvious in view of the '358 patent and the knowledge of a POSA.

The '358 patent also renders the additional limitation of claim 15 obvious. The '358 patent discloses pharmaceutical compositions comprising "one or more compounds of the present invention associated with at least one pharmaceutically acceptable carrier, diluent or excipient." (DTX-174 ('358 patent) at 9:31-34.) Further, the '358 patent recites "[a] pharmaceutical composition comprising a quantity of a compound according to claim 1 sufficient upon administration in a single or multiple dose regimen to reduce levels of TNF $\alpha$  in a mammal in combination with a carrier." (*Id.* at 22:36-39.) A POSA would have been motivated to prepare with a reasonable expectation of success to prepare the solid pharmaceutical composition recited in claim 15. Therefore, claim 15 is obvious in view of the '358 patent and the knowledge of a POSA.

Amgen attempts to rebut Defendants' *prima facie* obviousness of the asserted claims of the '101 patent as of March 20, 2002, by rehashing several arguments it makes with respect to the '638 patent. In particular, Amgen asserts that apremilast and enantiomerically pure apremilast are not found in the '358 patent. These arguments fail for the same reasons discussed above in Section IV.A.v.a.3. Amgen's other rebuttal arguments are lack of motivation to investigate crystalline forms of apremilast and a reasonable expectation of success. Both arguments fail. As discussed above, the '358 patent's teachings related to the pharmaceutical utility of the disclosed compounds would have motivated a POSA to formulate enantiomerically pure apremilast, which would in turn

have motivated a POSA to prepare and identify polymorphs of enantiomerically pure apremilast as a routine practice in the prior art for pharmaceutical and formulation research.

Amgen's argument against a reasonable expectation of success fares no better. As Dr. Steed will explain, the preparation and identification of polymorphs is both routine and predictable. This is because it was known that many pharmaceutical compounds exhibit polymorphism. Amgen relies heavily on a general concept of unpredictability in polymorphism. The mere fact that results of a polymorphic screening are not entirely predictable in advance, and must be confirmed through routine testing, does not mean that any obtained crystalline form is nonobvious. While a POSA may not have been able to predict with a mathematical certainty the exact crystalline forms obtained following a routine polymorphic screen, "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Amgen's argument is improper because it requires a POSA to know the existence and properties of the claimed crystalline apremilast Form B. *Id.*

**v. Other Prior Art Combinations Render Asserted Claims of the '101 Patent Obvious**

Clear and convincing evidence will show at trial that the teachings from ICH Guidelines, Byrn 1995, Byrn 1999, Brittain 1997, Brittain 1999, and Guillory, in view of each of the '358 patent, the '049 Publication, or the '052 Publication, would have further motivated a POSA to prepare a crystalline form of an enantiomerically pure apremilast with a reasonable expectation of obtaining the claimed crystalline apremilast Form B.

*First*, a POSA would have been motivated to prepare polymorphic forms of "enantiomerically pure" apremilast. It was known that pharmaceutical molecules commonly exhibited polymorphism. (See DTX-98 (Brittain 1997) at 1 ("[t]he occurrence of polymorphism

is quite common for organic molecules”).) Further, it was well known in the prior art that different crystalline polymorphs could affect the properties of a molecule intended for pharmaceutical use—*e.g.*, dissolution and bioavailability. (*See, e.g., id.* (“the Food and Drug Administration (FDA) requires that analytical procedures be used to detect polymorphic, hydrated, or amorphous forms of the drug substance”); *see also* DTX-128 (ICH Guidelines) at 12; DTX-103 (Byrn 1999) at 95 (“[i]f polymorphs exist then it is necessary to examine those physical properties of the different polymorphs that can affect dosage form performance (bioavailability and stability) or manufacturing reproducibility,” and that solubility is such a property).) Therefore, the regulatory authorities, such as FDA, set forth the requirement for identifying polymorphs of pharmaceutical products. (DTX-128 (ICH Guidelines) at 12.) Thus, the preparation and characterization of polymorphs became a routine process in pharmaceutical development.

The '358 patent, the '049 publication, and the '052 publication each disclose the pharmaceutical utility of apremilast and solid dosage forms containing compounds including apremilast. (*See, e.g.*, DTX-174 ('358 patent) at 7:1-23, 9:22-30; DTX-189 ('049 Publication) at 5, 9.) Therefore, a POSA would have been motivated to perform routine experiments to prepare and identify the different polymorphic forms of apremilast in view of the routine pharmaceutical development practice disclosed in the above prior art references. Further, the prior art references disclose the formation of solid material of racemic mixture containing apremilast (DTX-174 ('358 patent) at 9 (Example 12, disclosing “yellow solid” having a melting point of 144.0°C of a racemic mixture containing apremilast)), or solid enantiomerically pure apremilast. (*See* DTX-189 ('049 Publication) at 28-30 (Example 2); DTX-179 ('052 publication) at 15 (Example 2).) Thus, a POSA would have reasonably expected that apremilast exists in crystalline forms, and would have been motivated, with a reasonable expectation of success, to prepare crystalline solids of apremilast to

arrive at crystalline apremilast Form B.

*Second*, a POSA would have practiced routine prior art experimentation to prepare the crystalline Form B of “enantiomerically pure” apremilast. The prior art references disclose routine process experimentation that a POSA would practice for preparing polymorphs of apremilast. For example, Guillory discloses information “useful in devising a ‘screening’ protocol for the preparation of the various solid state forms of pharmaceuticals.” (DTX-125 (Guillory) at 7, 9-16.) Likewise, Byrn 1995 discloses a “Flow chart/decision tree for” preparing polymorphs. (DTX-102 (Byrn 1995) at 4.) Further, the prior art references disclose a limited number of solvents for polymorph preparation. For example, Byrn 1995 discloses the commonly used solvents including “water, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, ethyl acetate, hexane and mixtures if appropriate.” (*Id.* at 4.) Guillory discloses similar solvent systems. (DTX-125 (Guillory) at 10.)

*Third*, a POSA would have routinely collected the XRPD data recited in the Asserted Claims of the ’101 patent in accordance with the prior art. A POSA would have understood that XRPD was a standard analytical tool to establish the polymorphic identity of a pharmaceutical solid. (JTX-175 (Brittain 1999) at 9-12, 20-22, 25-30; *see also* DTX-128 (ICH Guidelines) at 12-13.) Further, it was known that the analytical data from the prior art methods discussed above were required for regulatory filing to FDA. (*See* DTX-128 (ICH Guidelines) at 12.)

Therefore, the Asserted Claims of the ’101 patent would have been obvious over ICH Guidelines, Byrn 1995, Byrn 1999, Brittain 1997, Brittain 1999, and Guillory in further view of the ’358 patent; or in further view of the ’049 Publication; or in further view of the ’052 Publication.

Amgen will raise similar arguments discussed above to rebut Defendants’ *prima facie*

obviousness of the Asserted Claims of the '101 patent. These arguments fail for the same reasons.

**vi. No Objective Indicia of Nonobviousness**

Amgen has not asserted any objective indicia of nonobviousness with respect to the claimed crystalline apremilast Form B recited in the Asserted Claims of the '101 patent. Thus, objective indicia of nonobviousness have no effect on the obviousness of the claimed crystalline apremilast Form B. *See Horizon Medicines*, 2020 WL 7022591, at \*3. To the extent Amgen relies on any other objective indicia discussed above in connection with the '638 patent or the '536 patent, those arguments fail for the same reasons.

**vii. The Asserted Claims of the '101 Patent Are Invalid under the Obviousness Type Double Patenting Doctrine.**

Amgen's patents run afoul of the obvious-type double-patenting doctrine, which "is designed to prevent an inventor from securing a second, later expiring patent for the same invention." *Abbvie v. Mathilda and Terence Kennedy*, 764 F.3d 1366, 1373 (Fed. Cir. 2014). The Federal Circuit has noted that this "problem" "exists" in a few contexts, including when "[p]atents claiming overlapping subject matter that were filed at the same time still can have different patent terms due to examination delays at the PTO." *Id.* (citing 35 U.S.C. § 154(b) (patent term adjustments)). "When such situations arise, the doctrine of obviousness-type double patenting ensures that a particular invention (and obvious variants thereof) does not receive an undue patent extension." *Id.* Thus, "the doctrine of obviousness-type double patenting continues to apply where two [post-URAA] patents that claim the same invention have different expiration dates." *Id.* at 1374; *see also Magna Electronics, Inc. v. TRW Automotive Holdings Corp.*, Nos. 1:12-cv-654, 1:13-cv-324, 2015 WL 11430786, at \*4-5 (W.D. Mich. Dec. 10, 2015) (following *Abbvie*, finding that a patent can act as double-patenting reference against another patent in the same family (*i.e.*, with the same priority date) where the patent at issue was set to expire after the reference patent

because of patent term adjustment).

Here, the Asserted Claims of the '101 patent are obvious in view of claim 1 of the '606 patent (JTX-220), as well as claim 1 of the '243 patent (JTX-10). Contrary to Amgen's assertion, the '606 patent and the '243 patent are proper double-patenting references against the '101 patent. The '101, '243, and '606 patents are all assigned to Amgen. The application leading to the '101 patent was filed on March 27, 2008, and the '101 patent is currently set to expire on December 9, 2023, because of a patent term adjustment. The application leading to the '243 patent was filed on December 10, 2013, and the application leading to the '606 patent was filed on March 26, 2015. Both the '606 and '243 patents expire on March 19, 2023. Because the '243 and '606 patents will expire earlier than the '101 patent, they can serve as a double-patenting reference to the '101 patent. *See Abbvie*, 764 F.3d at 1374; *see also Magna Electronics*, 2015 WL 11430786, at \*4-5.

The Federal Circuit decision in *Novartis AG v. Ezra Ventures LLC* does not change this conclusion. In *Novartis*, the Federal Circuit addressed whether an earlier-issued patent that received a patent term extension ("PTE"), which caused it to expire after a later-issued patent, was invalid for obviousness-type double patenting. *Novartis AG v. Ezra Ventures LLC*, 909 F.3d 1367 (Fed. Cir. 2018). The court determined "that obviousness-type double patenting does not invalidate a validly obtained PTE" where it is the "earlier-filed, earlier-issued [patent], not the later-filed, later-issued [patent], that has the later expiration date, due to a statutorily-allowed term extension under § 156." *Id.* at 1373-74. Here, Defendants have challenged the '101 patent's PTA—not a PTE granted under Section 156. *Novartis* is inapplicable because of statutory and policy differences between the PTA and the PTE. These differences underlie the Federal Circuit decision in *Merck & Co. v. Hi-Tech Pharmacal Co.*, 482 F.3d 1317 (Fed. Cir. 2007). The Federal Circuit noted the contrast between Section 156 for PTE and Section 154 for PTA, explaining that

Section 154 “expressly excludes patents in which a terminal disclaimer was filed from the benefit of a term adjustment for PTO delays” but Section 156 contains “no similar provision that excludes patents in which a terminal disclaimer was filed from the benefits of Hatch-Waxman extensions.” *Id.* at 1322. Thus, a PTE under Section 156 may be applied to a patent subject to a terminal disclaimer, while a PTA under Section 154 does not. *Id.* at 1324. In reaching this conclusion, the court explained that “[t]he purpose of the terminal disclaimer—to prevent extension of patent term for subject matter that would have been obvious over an earlier filed patent—remains fulfilled by virtue of the fact that the date from which any Hatch–Waxman extension is computed is the terminally disclaimed date.” *Id.* at 1323. Given that a terminal disclaimer obviates a double-patenting rejection or argument, and the different impact a terminal disclaimer has on a PTA and a PTE, it logically follows that a patent may be used as a double-patenting reference against another patent that expires later because of PTA. Therefore, the ’243 and ’606 patents can serve as double-patenting references against the ’101 patent.

Amgen has not argued, and cannot argue, that asserted claims 1 and 15 of the ’101 patent are not obvious in view of claim 1 of the ’243 patent or claim 1 of the ’606 patent. The limitations of claims 1 and 15 of the ’101 patent regarding the crystalline apremilast Form B are recited in identical form in claim 1 of the ’243 patent as well as in claim 1 of the ’606 patent. (*Compare* JTX-5 (’101 patent at claims 1 and 15), *with* JTX-10 (’243 patent at claim 1), *and* JTX-202 (’606 patent at claim 1).) As such, claim 1 of the ’243 patent and claim 1 of the ’606 patent each anticipate the claimed crystalline Form B of enantiomerically pure apremilast required by the Asserted Claims of the ’101 patent. If not anticipated, it would have at least been obvious to produce the claimed crystalline Form B of enantiomerically pure apremilast and to incorporate it into a solid pharmaceutical composition as recited in the Asserted Claims of the ’101 patent in

view of claim 1 of the '243 patent as well as in claim 1 of the '606 patent.

**viii. Amgen Cannot Establish that Zydus's Proposed ANDA Product Infringes the '101 Patent.**

Amgen cannot establish that, more likely than not, Zydus's proposed ANDA product, as it will be offered for sale, sold, used, and distributed in the United States or imported into the United States, will contain crystalline apremilast Form B, a necessity for infringing asserted claims 1 and 15 of the '101 patent. *See Ferring B.V. v. Watson Lab'ys, Inc.-Fla.*, 764 F.3d 1401, 1408 (Fed. Cir. 2014) (“[T]he ultimate infringement inquiry provoked by [an ANDA filing] is focused on a comparison of the asserted patent claims against the product that is likely to be sold following ANDA approval and determined by traditional patent law principles.”). Amgen's proof of infringement fails because it cannot, and will not, present any evidence that representative samples of Zydus's proposed ANDA product contain crystalline apremilast Form B. Instead, Amgen attempts to substitute testing of long-expired samples of Zydus's apremilast active pharmaceutical ingredient (“API”) and tablets in place of legitimate evidence of infringement. Amgen's expert Dr. Allan Myerson will argue that these long-expired samples somehow contain crystalline apremilast Form B, even though all four X-ray powder diffraction (“XRPD”) peaks required by claim 1 either cannot be seen or cannot be attributed to solely Form B.

Neither the parties nor the experts dispute that Zydus's proposed ANDA product contains crystalline apremilast Form A. (Zydus Stipulated Facts at ¶¶ 14-15.) Zydus's API specification requires XRPD peaks associated with Form A and Amgen has asserted the '283 patent covering crystalline apremilast Form A against Zydus. It is undisputed that to infringe the asserted claims of the '101 patent, all four XRPD peaks recited in the claim must be present and attributable to Form B in a diffractogram from a representative sample of the apremilast product that Zydus will sell in the United States—Zydus's proposed ANDA product.

**a. Amgen's XRPD testing was not performed on representative samples of Zydus's proposed ANDA product.**

In order for Zydus to sell its proposed ANDA product, that product must meet the release specifications described in Zydus's ANDA. If a sample of Zydus's tablets does not comply with those specifications, it cannot be sold and thus would not be representative of Zydus's proposed ANDA product. See *Merck Sharp & Dohme Corp. v. Amneal Pharms. LLC*, 881 F.3d 1376, 1385 (Fed. Cir. 2018) (“[T]he critical inquiry is whether [what has been tested] is representative of what is likely to be approved and marketed.”); *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997) (Infringement “must focus on what the ANDA applicant will likely market if its application is approved.”). At trial, Dr. Myerson will readily concede that he does not rely on any of Zydus's internal testing conducted on Zydus's apremilast API or proposed ANDA product samples despite the fact that these are the only available XRPD data concerning representative samples.

Amgen's entire infringement case for the '101 patent rests on third-party testing of samples of Zydus's API and tablets that was conducted thirty months and eleven months after their expiration, respectively. As FDA explained in a recent guidance, such samples are not considered representative of the ANDA product and therefore cannot be used for obtaining approval of an ANDA. See *Guidance for Industry: Development of Abbreviated New Drug Applications During the COVID-19 Pandemic – Questions and Answers* (Apr. 5, 2021) available at <https://www.fda.gov/media/147355/download> at 4 (noting that expired reference batches of proposed ANDA products are generally not suitable for use in completing bioequivalence studies required for ANDA approval because “the safety and effectiveness of the product beyond the labeled expiration date is not known”); see also *id.* (“A drug product's expiration date, as determined by appropriate stability testing, provides assurance that the drug product meets the

applicable standards of identity, strength, quality, and purity at the time of use.”) (citing 21 C.F.R. § 211.137).

Zydus produced API and tablet samples to Amgen between November 2018 and March 2019, well in advance of the proposed ANDA product’s twenty-four-month expiry that ended on July 31, 2019. Yet the samples were held in Amgen’s counsel’s offices for nearly a year until May 2020. Amgen cannot, and makes no attempt to, account for why testing was delayed until after the samples had expired. In addition, Amgen cannot, and makes no attempt to, identify or describe the exact storage conditions of the samples while they were in its counsel’s custody for nearly a year. Perhaps, Amgen believed that waiting as long as it could before having the samples tested might be its best chance of arguing infringement, even though “[e]vidence derived from expired tablets is not relevant to the question of what will be sold.” *SmithKline Beecham Corp. v. Apotex Corp.*, 98 C 3852, 2002 WL 1613724, at \*2 (N.D. Ill. July 17, 2002); *see also Merck Sharp & Dohme Corp. v. Teva Pharms. USA, Inc.*, 217 F. Supp. 3d 782, 797 (D. Del. 2016) (“[E]xpired samples are not representative of the ANDA product.”).

Despite the samples’ expiration, and storage under undisclosed conditions, Dr. Myerson and Amgen’s testing expert, Dr. Fabia Gozzo, will freely admit that Amgen never sought to determine whether Zydus’s API and tablet samples met their required release specifications. In other words, neither Dr. Gozzo nor Dr. Myerson can attest that Dr. Gozzo conducted testing on representative samples. Thus, the Court should not give any weight to Dr. Gozzo’s XRPD testing or any testimony regarding its results.

**b. Amgen cannot establish that the expired samples tested by Dr. Gozzo contained crystalline apremilast Form B.**

Zydus’s polymorph expert, Dr. Steven Miller, will explain that while Dr. Gozzo’s XRPD testing confirms that the expired samples contain crystalline apremilast Form A, it fails to provide

evidence that the samples contain Form B as described in the specification and asserted claims 1 and 15 of the '101 patent. Rather, the XRPD peaks that Dr. Myerson argues establish infringement of the '101 patent can all be attributed to other crystalline forms of apremilast, including Form A or Form F.

To infringe a patent claim containing specific analytical characteristics, such as XRPD peaks, it must be established that all claimed peak values can be identified and attributed to the allegedly infringing material. *See Zenith Labs., Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1423-24 (Fed. Cir. 1994). Here, Dr. Miller will show that of the four peaks listed in claim 1, peaks appearing at approximately three of those locations ( $10.1$ ,  $13.5$ , and  $26.9 \pm 0.2^\circ 2\theta$ ) are found in the reference sample of crystalline apremilast Form A tested by Dr. Gozzo—a fact confirmed by Amgen's experts. In fact, when overlaying Dr. Gozzo's XRPD diffractograms of Zydus's expired API and tablet samples with reference samples of crystalline apremilast Forms A and B, three peaks in Zydus's samples that Dr. Myerson identifies as proving the presence of Form B ( $10.1$ ,  $13.5$ , and a peak he assigns a value of  $26.9$  but is actually at  $26.5, \pm 0.2^\circ 2\theta$ ) *all correspond with peak locations and shapes for Form A and not Form B*. On the other hand, when Dr. Gozzo compared the diffractogram of Amgen's Form B reference standard to the diffractograms of Form B in the '101 patent specification, she was able to identify all four claim 1 peaks with identical peak locations and shapes as depicted in the specification. Dr. Myerson ignores these critical differences in peak location and shape, which Dr. Gozzo's experiments were definitively able to resolve.

Even setting aside the issues of peak location and shape, Dr. Gozzo's diffractograms show (and Dr. Myerson admits) that one or more of the peaks required by claim 1 do not appear in Zydus's tablet ( $20.7$  and  $26.9 \pm 0.2^\circ 2\theta$ ) and API ( $26.9 \pm 0.2^\circ 2\theta$ ) samples. Even if the samples

were shown to be representative, which they are not, the absence of any claim 1 peak requires a finding of no infringement. *See Glaxo*, 110 F.3d at 1566 (rejecting patentees' attempt to show infringement with a single peak because it ignored claim limitations requiring other peaks).

Amgen will argue that the failure to see the claimed peaks in the samples should not matter, because those peaks could be obscured by overlapping peaks from other forms of apremilast or excipients present in the samples. Dr. Miller, however, will show that all of the other peaks Dr. Myerson points to in the diffractograms of Zydus's samples are either consistent with Form B or can also be found in either the Form A reference sample or Form F as described in the patent specification. Indeed, Amgen's experts both admit they did not conduct testing using Dr. Gozzo's purportedly sensitive synchrotron equipment or other analysis of Form F to determine whether it presents overlapping XRPD peaks with Form B. As Dr. Miller will explain, it cannot be determined that, more likely than not, Form B is present in the expired Zydus samples, given the evidence in the record concerning overlapping peaks found in other crystalline forms of apremilast.

Amgen cannot meet its burden of proving that Zydus's proposed ANDA product, as it will be sold, would infringe claims 1 and 15 of the '101 patent by a preponderance of the evidence. Therefore, the Court must find that Zydus does not infringe the asserted claims of the '101 patent.

#### **D. The '541 Patent**

The asserted claims of the '541 patent generally recite a method for treating psoriasis by administering stereomerically pure apremilast according to a particular dosing titration schedule. The earliest effective filing date for the '541 patent is 2014, and Defendants will present clear and convincing evidence that the asserted claims would have been obvious to a POSA as of this date. At that time, a POSA would have been motivated, with a reasonable expectation of success to: (1) to administer stereomerically pure apremilast for the treatment of psoriasis; and (2) start with 10 mg in the morning on day one and titrate the dose upwards by 10 mg per day until reaching the

target dose of 30 mg bid (twice per day) on day six.

*First*, stereomerically pure apremilast was known and disclosed in the prior art as of 2014. The '536 patent, as discussed, specifically disclosed and claimed stereomerically pure apremilast and its use for treating psoriasis. (JTX-7 ('536 patent) at 30:64-31:3 (Claim 1).)

*Second*, the prior art taught that the most effective dose of apremilast for treating moderate to severe plaque psoriasis was 30 mg bid, and that the dose would need to be titrated over the first week to mitigate dose-dependent gastrointestinal-related side effects. (DTX-153 (Papp 2012) at 2.) In the Papp 2012 study, patients were administered 10 mg bid on day one, and the dosage was increased by 20 mg every other day until the target dose of 30 mg bid was reached on day five. (*Id.*) A POSA would have been motivated to further extend the titration schedule to improve tolerability, and it would have required only routine optimization to arrive at the claimed titration schedule. *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (“Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.”) (quotations omitted); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007) (“[T]he discovery of an optimum value of a variable in a known process is usually obvious”). Indeed, other prior art available as of 2014 taught titrating apremilast over seven days, which did not have any reported impact on efficacy and achieved the same goal of reducing side effects. (*See, e.g.*, DTX-162 (Schett 2012) at Abstract, 2-3.) Amgen’s arguments otherwise are unpersuasive, and tellingly, Amgen presents no evidence or arguments that any secondary considerations show the claimed titration schedule was nonobvious, further underscoring the lack of novelty of the claimed invention. *See Horizon Medicines*, 2020 WL 7022591 at \*3.

**i. The Asserted Claims of the '541 Patent**

Asserted claims 2, 19, and 21 of the '541 patent read:

2. A method for treating a patient with stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, wherein the patient is suffering from psoriasis, the method consisting of:
  - (a) administering to the patient stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione in an initial titration dosing schedule consisting of
    - (i) 10 mg in the morning on the first day of administration;
    - (ii) 10 mg in the morning and 10 mg after noon on the second day of administration;
    - (iii) 10 mg in the morning and 20 mg after noon on the third day of administration;
    - (iv) 20 mg in the morning and 20 mg after noon on the fourth day of administration;
    - (v) 20 mg in the morning and 30 mg after noon on the fifth day of administration; and
  - (b) on the sixth and every subsequent day, administering to the patient 30 mg in the morning and 30 mg after noon of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione.
19. The method in any one of claims 1-14, wherein the stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione comprises greater than about 98% by weight of the (+) isomer of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione based on the total weight percent of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione.
21. A method as in any one of claims 1-14, wherein the stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is administered in tablet form.

(JTX-13 at 31:3-26; 36:22-29, 38-41 (claims 2, 19, 21)).

## ii. The Asserted Claims of the '541 Patent Would Have Been Obvious

Clear and convincing evidence will show that the subject matter of claims 2, 19, and 21 of the '541 patent would have been obvious to a POSA as of the 2014 effective filing date over (1)

Papp 2012 and the '536 patent, in view of Schett 2012 and knowledge of a POSA; (2) Papp 2012 and the '536 patent, in view of Schett 2012, in further view of ICH 1994, and knowledge of a POSA; (3) the '536 patent and Papp 2012, and knowledge of a POSA; and/or (4) '536 patent and Schett 2012, and knowledge of a POSA.

The '541 patent is situated differently from the other Patents-in-Suit because of its significantly later effective filing date of 2014. In other words, given that the other Patents-in-Suit, including the '536 patent, already issued and are thus prior art to the '541 patent, there is no dispute that stereomerically pure apremilast, including apremilast comprising greater than 98% by weight of the (+) isomer, was disclosed and known in the prior art as of 2014. There is also no dispute that it was known that apremilast was effective in treating psoriasis, and that the dose needed to be titrated to mitigate the risk of gastrointestinal-related side effects. The only alleged novelty of the claimed invention is the titration schedule itself. But for the reasons discussed below, the claimed titration schedule is simply routine optimization of the prior art. *In re Applied Materials, Inc.*, 692 F.3d at 1295; *Pfizer*, 480 F.3d at 1368. Tellingly, Amgen has not asserted any secondary considerations of nonobviousness, further highlighting the obviousness of the asserted claims. *See Horizon Medicines*, 2020 WL 7022591 at \*3.

**a. It is undisputed that the stereomerically pure claim limitations in claims 2 and 19 of the '541 patent are disclosed in the '536 patent.**

The stereomerically pure claim limitations in the asserted claims of the '541 patent are:

- “stereomerically pure [apremilast]” (claim 2); and
- “stereomerically pure [apremilast] comprises greater than about 98% by weight of (+) isomer based on the total weight percent of the compound” (claim 19).

The '536 patent discloses each of these limitations, and Amgen does not dispute otherwise. For example, claims 1 and 6 of the '536 patent recite stereomerically pure apremilast, including

where stereomerically pure apremilast comprises greater than 97% by weight of the (+) isomer. (JTX-7 ('536 patent) at 30:64-31:3 (Claim 1); *see also id.* at 31:14-16 (Claim 6).) Based on the disclosures in the '536 patent, a POSA would have been motivated with a reasonable expectation of success to use and administer to patients stereomerically pure apremilast, including stereomerically pure apremilast comprising greater than about 98% by weight of (+) isomer.

As a practical matter, an optical purity greater than 97% means that the purity level falls within the range of 97% to 100%, including 98% to 100% pure, as required by claim 19 of the '541 patent. Because the claimed purity overlaps with the prior art, "the burden of production falls upon the patentee to come forward with evidence that: (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations." *Galderma*, 737 F.3d at 738. Amgen cannot make, and has not made, this showing. Indeed, Amgen has not alleged any teaching away or secondary considerations arriving from the claimed enantiomeric purity levels.

In any event, a POSA developing a chiral pharmaceutical product would have been motivated to make it as optically pure as possible, including with an optical purity of 100%, and administer that to patients. It would have simply been a matter of routine experimentation for a POSA to do so as of the 2014 effective filing date. Expert testimony will show that at that time, a POSA would have known that chiral column chromatography, chiral acid separation, and asymmetric synthesis could yield a single isomer of a compound having greater than 98% optical purity.

As such, the '536 patent discloses stereomerically pure apremilast, including stereomerically pure apremilast comprising greater than 98% of the (+) isomer, as recited in the asserted claims of the '541 patent.

**b. The claimed dosing titration schedule would have been obvious.**

By the time the '541 patent was filed in 2014, apremilast was well into clinical development for multiple disease states, and the prior art specifically taught that it was safe and effective for treating patients with moderate to severe psoriasis. For example, Papp 2012 disclosed a phase IIb study sponsored by Celgene, the purpose of which was to investigate “the clinical efficacy and safety of apremilast 10, 20, and 30 mg twice daily versus placebo in patients with moderate to severe plaque psoriasis” in a phase IIb study sponsored by Celgene. (DTX-153 (Papp 2012) at 1-2.)

Papp 2012 taught that patients were “randomly assigned in a 1:1:1:1 ratio to oral apremilast 10 mg twice daily, apremilast 20 mg twice daily, apremilast 30 mg twice daily, or placebo.” (*Id.* at 2.) In particular, the “[d]oses were titrated in the first week to mitigate potential dose-dependent adverse events of apremilast; all patients reached the target dose by day 5.” (*Id.*) The results from the Papp 2012 study showed that apremilast “given orally at 20 mg or 30 mg twice daily, seems to be efficacious, safe, and tolerable for patients with moderate to severe plaque psoriasis.” (*Id.* at 7.) In addition, because “apremilast 30 mg had the most favourable outcome,” this dose was “being investigated for patients with moderate to severe plaque psoriasis in phase 3 trials.” (*Id.*)

In Papp 2012, “the rate of overall reported adverse events was generally related to dose,” with “[h]e headache, nausea, and diarrhoea [being] the most frequently reported with apremilast 30 mg; at least half of these events occurred within the 2 weeks of treatment initiation and resolved within a week.” (*Id.*) Nevertheless, apremilast was generally well tolerated, and there were “[n]o serious adverse events, malignancies, major cardiovascular events, or serious infections [] deemed to be related to apremilast treatment.” (*Id.*)

Thus, in light of the teachings of Papp 2012, a POSA would have known that 30 mg of apremilast administered twice daily was the most effective dose for treating psoriasis, and Amgen cannot credibly dispute otherwise. (*Id.*) Amgen also does not dispute that although apremilast was generally well tolerated, it was known to be associated with certain dose-dependent, gastrointestinal-related side effects—*e.g.*, nausea and diarrhea. (*Id.*) Accordingly, and consistent with the teachings of Papp 2012 and other similar clinical trial publications by Celgene, a POSA would have recognized the need to titrate the dose of apremilast during the first week of treatment to mitigate these gastrointestinal side effects. (*Id.* at 2.) Other prior art available as of the 2014 effective filing date further confirm the teachings in Papp 2012 regarding dose titration to avoid adverse effects in additional disease conditions, such as psoriatic arthritis, Behçet’s disease, and ankylosing spondylitis. (See DTX-483 (Clinical Trial No. NCT ’734 v. 8) at 2 (“In an effort to mitigate the dose-dependent adverse effects of apremilast (*e.g.*, headache or gastrointestinal disturbances), participants had their dose titrated over a 7-day period (Days 1 through 7).”); DTX-93 (Clinical Trial No. NCT ’359 v.6) at 4 (disclosing that during treatment phase days 1–7, the dose was titrated from 10 mg BID to 30 mg BID); DTX-201 (Clinical Trial No. NCT ’092 v. 6) at 3 (“To ameliorate the dose dependent adverse events of CC-10004 (headache and GI disturbances) there will be dose titration of 10 mg od (or placebo) for days 1-3 followed by 20 mg od (or placebo) days 4 to 7 in the first week of dosing.”); DTX-109 (Clinical Trial No. NCT ’264) at 3 (disclosing administration of apremilast “10 mg tablets with dose titration to 30 BID for 169 days”); DTX-162 (Schett 2012) at 2 (“Dose escalation was implemented during the first 7 days of treatment in an attempt to decrease the likelihood of adverse events (AEs) related to treatment initiation.”); DTX-157 (Pathan 2012) at 2 (“Patients were started on apremilast 10 mg twice daily

or placebo and the dose was titrated by 20 mg every 2 days until the maximum dose of 30 mg twice daily was achieved on day 5.”.)

Indeed, both as of 2014 and today, it is common and routine to titrate the dose of a drug that may be associated with treatment-related side effects. For example, Neurontin® (gabapentin) (which was FDA-approved before 2014) is a medication that is prescribed for patients with chronic itch and has a wide dose range (up to 2700 mg/day). Expert testimony will show that because patients can feel dizziness and other side effects when they first begin treatment, physicians typically start with a low dose (300 mg) and titrate the dose upwards to improve tolerability. Dose escalation is commonly done with other drugs as well. (See JTX-227 (Simonneau 2012) at 2 (teaching that eligible patients “received selexipag 200 µg twice daily . . . or matching placebo on day 1. Dosage was then up-titrated to 400 µg twice daily on day 3, to 600 µg twice daily on day 7, and 800 µg twice daily on day 21.”); DTX-145 (NAMENDA 2013 Label) at 2 (“The dose should be increased in 5 mg increments to 10 mg/day (5 mg twice daily), 15 mg/day (5 mg and 10 mg as separate doses), and 20 mg/day (10 mg twice daily); DTX-195 (WO ’372) at 18:21-23 (teaching that the dose of masitinib “can be dose escalated by increments of 1.5 mg/kg/day to reach a maximum of 9.0 mg/kg/day in low responder patients.”).)

In Papp 2012, the dose was titrated until patients “reached the target dose by day 5.” (DTX-153 (Papp 2012) at 2.) Amgen argues that because Papp 2012 is not clear on the exact time of day of the dosing of the drug, a POSA would not know whether Papp 2012 disclosed any particular dosing titration schedule, let alone a fixed titration schedule. However, Papp 2012 taught that (i) the doses administered were 10 mg, 20 mg, and 30 mg bid, (ii) the target dose was 30 mg bid, and (iii) the dose was titrated over five days. Defendants’ experts will testify that based on this information, a POSA would have readily understood that Papp 2012 disclosed the following

fixed dose titration schedule for patients being treated with 30 mg of apremilast twice a day (once am and once pm), as compared with the titration schedule recited in the '541 patent:

	<b>Papp 2012</b>			<b>'541 Patent (claim 2)</b>		
	<b>1st Dose (mg)</b>	<b>2nd Dose (mg)</b>	<b>Total dose (per day)</b>	<b>1st Dose (mg)</b>	<b>2nd Dose (mg)</b>	<b>Total dose (per day)</b>
Day 1	10	10	20	10	0	10
Day 2	10	10	20	10	10	20
Day 3	20	20	40	10	20	30
Day 4	20	20	40	20	20	40
Day 5	30	30	60	20	30	50
Day 6 (and thereafter)	30	30	60	30	30	60

Celgene's Pathan 2012 article disclosed the exact same dosing schedule for the administration of apremilast in a phase II study to treat patients with ankylosing spondylitis, an inflammatory condition that is similarly caused by overactivation of the TNF $\alpha$  pathways—a fact that Amgen does not dispute. (DTX-157 (Pathan 2012) at 2.) Indeed, Pathan 2012 provides that in light of apremilast's demonstrated efficacy in treating patients with psoriasis and psoriatic arthritis, and "[g]iven that cytokines influenced by PDE4 [also] play an important role in spondyloarthritis," there "is a rationale to explore apremilast use" in ankylosing spondylitis. (*Id.* at 1-2.) Expert testimony will show that a POSA would have considered the teachings of Pathan 2012, thereby further confirming the titration schedule administered in Papp 2012.

There are three primary differences between the dosing schedule recited in Papp 2012 and that required by the asserted claims of the '541 patent: (i) Papp 2012 starts with 10 mg twice daily, as opposed to 10 mg in the morning; (ii) the titration schedule in Papp 2012 increases by increments of 20 mg every other day instead of 10 mg per day; and (iii) the dose in Papp 2012 was titrated over 5 days instead of 6 days. Clear and convincing evidence will show that each of these differences is trivial, and it would have been well within the skill of a POSA as of the 2014 effective

filing date to modify the titration schedule taught by Papp 2012 to improve tolerability, and arrive at the dosing scheme claimed by the '541 patent. *In re Applied Materials, Inc.*, 692 F.3d at 1295; *Pfizer*, 480 F.3d at 1368. A POSA would have reasonably expected that doing so would further improve the risk or severity of gastrointestinal-related side effects from administering apremilast.

*First*, it would have been obvious, as a matter of routine exercise, start with 10 mg of apremilast in the morning and increase the dose by 10 mg per day until reaching the target dose of 30 mg twice per day. A POSA would have known that the lowest dose of apremilast administered in the prior art was 10 mg per day. For example, Schett 2012 discloses a phase II study investigating the efficacy and safety of 20 mg apremilast twice per day (or 40 mg once per day) in patients with psoriatic arthritis. (DTX-162 (Schett 2012) at 1.) Schett 2012 provides that “[d]ose escalation was implemented during the first 7 days of treatment in an attempt to decrease the likelihood of adverse events (AEs) related to treatment initiation.” (*Id.* at 2.) NCT '092, which is incorporated by reference in Schett 2012 and was published before the 2014 effective filing date, confirms that patients in Schett 2012 were administered apremilast according to the following schedule:

	<b>Dose</b>
Day 1	10 mg
Day 2	10 mg
Day 3	10 mg
Day 4	20 mg
Day 5	20 mg
Day 6	20 mg
Day 7	20 mg
Day 8 (and thereafter)	40 mg or 20 mg BID

(*See* DTX-201 (Clinical Trial No. NCT '092 v. 6) at 3; DTX-92 (Clinical Trial No. NCT '092 v. 7) at 3.) Thus, Schett 2012 discloses initiating treatment with 10 mg per day of apremilast and increasing the dose by 10 mg increments to mitigate the risk of dose-dependent side effects.

In light of the teachings of Papp 2012 and Schett 2012, a POSA would have been motivated to start with a single dose of 10 mg on the first day and to increase the dose in even increments of 10 mg per day to further improve tolerability of gastrointestinal side effects in patients taking apremilast. A POSA would have further had a reasonable expectation of success of doing so, given the prior art '536 patent's disclosures that "[s]uitable dosing regimens can be readily selected by those skilled in the art with due consideration of" factors that "vary according to the age, body weight, and response of the individual patient." (JTX-7 ('536 patent) at 13:45-49.)

*Second*, it would have been obvious to a POSA to titrate the dose of apremilast over 6 days as claimed. If a POSA started treatment with 10 mg, and increased it by 10 mg per day, as taught by Papp 2012, the '536 patent, and Schett 2012, the patient would necessarily reach the target dose of 30 mg bid by the sixth day. Moreover, Papp 2012 discloses dose titration over the first five days of treatment in psoriasis patients (DTX-153 at 2), while Schett 2012 teaches titrating over seven days (DTX-162 at 2), both of which were able to mitigate side effects without affecting efficacy. A POSA would have been motivated to tweak the dosage schedule in Papp 2012 and titrate apremilast over a longer period of time to further lessen the risk or severity of side effects. Because there were a "finite number of known choices in the prior art," and a "reasonable expectation of success for the choice that is tried," it would have been obvious for a POSA to try titrating over six days. *Hoffman-La Roche Inc. v. Apotex, Inc.*, 748 F.3d 1326, 1340 (Fed. Cir. 2014). A POSA would have had a reasonable expectation of success of doing so given that dose titration is a routine exercise, and in light of the teachings of Schett 2012 where apremilast was successfully titrated over seven days of treatment.

ICH 1994 further confirms that it would have only required routine experimentation for a POSA to arrive at the dosing titration schedule as claimed. ICH 1994 teaches that dose-

concentration and/or dose-response information is routinely “used to prepare dosage and administration instructions in product labeling.” (JTX-229 (ICH 1994) at 4.) ICH 1994 provides that dose-response information is also helpful for choosing the starting dose of a drug. In particular, the “[s]election of dose is best based on that information, together with a judgment about the relative importance of desirable and undesirable effects.” (*Id.*) For example, a high starting dose “might be a poor choice for a drug with a small demonstrated separation between its useful and undesirable dosage ranges. In these cases, the recommended starting dose might best be a low dose exhibiting a clinically important effect in even a fraction of the patient population, with the intent to titrate the dose upwards as long as the drug is well-tolerated.” (*Id.*)

Accordingly, it would have been obvious to treat a patient suffering from psoriasis by administering stereomerically pure apremilast in an initial titration dosing scheduling consisting of: (i) 10 mg in the morning on the first day of administration; (ii) 10 mg in the morning and 10 mg after noon on the second day; (iii) 10 mg in the morning and 20 mg after noon on the third day; (iv) 20 mg in the morning and 20 mg after noon on the fourth day; (v) 20 mg in the morning and 30 mg after noon on the fifth day; and (vi) 30 mg in the morning and 30 mg after noon on the sixth and every subsequent day, as recited in the asserted claims of the '541 patent. A POSA would have been motivated to administer apremilast to patients in this manner and would have had a reasonable expectation of success that such administration would successfully mitigate gastrointestinal-related side effects.

Dependent claim 21 further requires that “the stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisindoline-1,3-dione is administered in tablet form.” However, the '536 patent discloses compositions of apremilast “that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets

(e.g., chewing tablets), caplets, capsules, and liquids (e.g., flavored syrups).” (JTX-7 (’536 patent) at 16:22-26.)

**iii. No Objective Indicia of Nonobviousness**

Amgen has not asserted any objective indicia of non-obviousness with respect to the asserted claims of the ’541 patent. Thus, objective indicia of nonobviousness have no effect on the obviousness of the asserted claims of the ’541 patent. *See Horizon Medicines*, 2020 WL 7022591 at \*3.

**iv. The Alleged Evidence of “Unexpected Results” Presented During Prosecution of the ’541 Patent Does Not Support the Non-Obviousness of the Asserted Claims**

As noted above, Amgen has not contended that any secondary considerations, including unexpected results, support the non-obviousness of the ’541 patent. Nevertheless, during prosecution of the ’541 patent, the applicant asserted unexpected results based on a comparison of the adverse events reported in Kavanaugh 2014 (using the claimed titration schedule) to the prior art Papp 2012 and Schett 2012 studies. Expert testimony will show that the applicant’s comparisons of these adverse events failed to properly account for the differences in patient populations and measurement of adverse events in all three studies. Moreover, a properly-conducted statistical analysis indicates that there is no statistical difference in the number of adverse events or withdrawals due to adverse events as a result of administering apremilast according to the claimed titration schedule. Indeed, Defendants’ experts will testify that it would have been entirely expected that extending the titration schedule over the prior art would reduce the incidence of adverse events. *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (“Results which differ by percentages are differences in degree rather than kind, where the modification of the percentage is within the capabilities of one skilled in the art at the time.”); *see also In re Sebela Patent Litig.*, 2017 WL 3449054, at \*24 (D.N.J. Aug. 11, 2017) (finding no

unexpected results where a POSA considering the prior art “would reasonably expect that side effects would decrease as doses decreased, particularly in light of the general understanding that if you lower the dose of a drug, side effects decrease.”).

**v. Amgen Cannot Prove that Pharmascience Will Infringe Claims 2, 19 or 21 of the '541 Patent.**

Amgen, as the patent holder, has the burden of proving that all elements of the asserted claims are present in the accused product. *See Jazz Photo Corp. v. ITC*, 264 F.3d 1094, 1102 (Fed. Cir. 2001); *Laitram Corp. v. Rexnord, Inc.*, 939 F.2d 1533, 1535 (Fed. Cir. 1991) (holding that the patentee must demonstrate every limitation of every claim). The burden of proof on infringement never shifts to the defendant. *Imhaeuser v. Buerk*, 101 U.S. 647, 662 (1879) (“[T]he burden to prove infringement never shifts if the charge is denied in the plea or answer.”).

Amgen accuses Pharmascience of inducing infringement and contributing to infringement of claims 2, 19 and 21 of the '541 patent through the distribution of its finished dosage form and product label. Ex. B1, Amgen's CFI at ¶ 1. Claim 2 (from which claims 19 and 21 depend) recites a method of treating psoriasis “consisting of” administering stereometrically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione (apremilast) following the below dosage schedule:

- (a) an initial dosing schedule “consisting of”:
  - (i) 10 mg in the morning on the first day of administration;
  - (ii) 10 mg in the morning and 10 mg after noon on the second day of administration;
  - (iii) 10 mg in the morning and 20 mg after noon on the third day of administration;
  - (iv) 20 mg in the morning and 20 mg after noon on the fourth day of administration;
  - (v) 20 mg in the morning and 30 mg after noon on the fifth day of administration; and

(b) on the sixth and every subsequent day, administering to the patient 30 mg in the morning and 30 mg after noon of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione.

Ex. E1, Pharmascience's CFN at ¶ 64; JTX-0013. The patent thus uses "consisting of" twice: once to limit the treatment of psoriasis to the administration of stereometrically pure apremilast, and then again to limit the dosing schedule to the recited days and amounts.

There are three established "transitional phrases" used in patent claim drafting: (i) comprising, (ii) consisting essentially of, and (iii) consisting of. Where, as here, the transitional phrase "consisting of" is used, an accused method must have *only* the elements or steps recited in the claim. *In re Gray*, 53 F.2d 520, 11 USPQ 255 (CCPA 1931) (explaining that the transitional phrase "consisting of" excludes any element, step, or ingredient not specified in the claim). If any other element or step is present, then the accused method does not infringe. *See Multilayer Stretch Cling Film Holdings, Inc., v. Berry Plastics Corp.*, 831 F.3d 1350, 1358 (Fed. Cir. 2016).

Whether an accused product satisfies a "consisting of" limitation is a question of fact resolved in determining infringement. *See Amgen Inc. v. Amneal Pharm. LLC*, 945 F.3d 1368, 1378 (Fed. Cir. 2020) ("the normal restricting meaning of the 'consisting of' language settle[s] the infringement issue"). When asked to construe such established transition terms, courts have generally declined to provide any further construction beyond the well-established legal meaning of the term. *See, e.g., Depomed, Inc. v. Sun Pharma Global FZE*, Civ. No. 11-3553 (JAP), 2012 WL 3201962, at \*13 (D.N.J. Aug. 3, 2012); *Biovail Labs. Int'l SRL v. Abrika, LLLP*, No. 04-61704, 2006 WL 6111777, at \*18 (S.D. Fla. Aug. 24, 2006); *Classified Cosmetics, Inc. v. Del Labs., Inc.*, No. 03-4818, 2004 WL 5645578, at \*5 (C.D. Cal. June 14, 2004).

In order to establish induced infringement, Amgen must show that (1) there is direct infringement, (2) Pharmascience actively encouraged the infringement, and (3) Pharmascience knew that the acts it induced constituted patent infringement. *See e.g., Power Integrations, Inc. v.*

*Fairchild Semiconductor Int'l, Inc.*, 843 F.3d 1315, 1332 (Fed. Cir. 2016). If an accused infringer promotes its product for multiple uses, some of which fall within the asserted claim and some of which do not, there is no induced infringement because there is no “active encouragement” of infringement. See *HZNP Medicines LLC v. Actavis Labs. UT, Inc.*, 940 F.3d 680, 940 F.3d at 701 (citing *Takeda Pharm. U.S.A. Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 630-31 (Fed. Cir. 2015)); see also *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006) (en banc) (“[I]nducement requires evidence of culpable conduct, directed to encouraging another’s infringement, not merely that the inducer had knowledge of the direct infringer’s activities.”).

In order to establish contributory infringement, Amgen must show that (1) there is direct infringement, (2) Pharmascience knew that its product was being made for a patented and infringing use, (3) Pharmascience’s product has no substantial non-infringing uses, and (4) Pharmascience’s product is a material part of the invention. *Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321, 1326 (Fed. Cir. 2010) (citing 35 U.S.C. § 271(c)). Likewise here, if an accused infringer promotes its product for multiple uses, some of which fall within the asserted claim and some of which do not, there is no contributory infringement because there are “substantial noninfringing uses.” See 35 U.S.C. § 271(c); see also *Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1312 (Fed. Cir. 2005).

Here, Amgen cannot carry its burden of proving infringement because Pharmascience’s prescribing information promotes use of Pharmascience’s ANDA product for multiple uses, at least some of which fall *outside* the asserted claim. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Amgen has no competent evidence that Pharmascience either induces or contributes to the specific, narrow psoriasis treatment regimen recited in the claims.

**a. Administration of Pharmascience's ANDA Product According to Pharmascience's Label Does Not Induce or Contribute to a Method of Treating Psoriasis Consisting of Administering Stereometrically Pure Apremilast According to the Claimed Dosage Schedule**

The asserted claims require that the method of treating psoriasis consist of administering stereometrically pure apremilast according to a specific dosage schedule. JTX-0013. Pharmascience's label does not instruct that the Pharmascience ANDA product be administered in such a limited fashion. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**1. Pharmascience's Label Is, At Best, Agnostic as to Whether Apremilast Is Administered as a Monotherapy (as Required by the Claims) or as Part of a Combination Therapy.**

Amgen's claims are limited to a psoriasis treatment "consisting of" administering stereometrically pure apremilast on a particular dosing schedule. The claims thus exclude methods

of psoriasis treatment that include other therapies (like phototherapy or administering other drugs) *in addition to* administering apremilast. Administering multiple therapies to a patient is called combination therapy. Administering one therapy alone is called monotherapy.

[REDACTED]

Where a label is agnostic about whether to practice an infringing or noninfringing method, it does not induce infringement as a matter of law. *See, Takeda Pharms. U.S.A., Inc. v. W.-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015); *Shire LLC v. Amneal Pharmaceuticals, LLC*, 2014 WL 2861430, at \*5 (D.N.J. 2014) (finding no inducement of a method of administering a drug with food, where the label stated that the drug could be taken “with or without food”), affirmed in relevant part, 802 F.3d 1301 (Fed. Cir. 2015). It is not sufficient that the label merely describes “an infringing mode.” *Takeda Pharms. U.S.A., Inc.*, 785 F. 3d at 631 (citation omitted). Indeed, “it is well-established that mere knowledge of possible infringement by others does not amount to inducement.” *Id.*; *Cf. Otsuka Pharm. Co., Ltd. v. Torrent Pharms. Ltd., Inc.*, 99 F. Supp. 3d 461, 490 (D.N.J. 2015) (“[C]ourts have repeatedly found incidental references to even

infringing uses . . . insufficient to constitute instruction or encouragement, . . . as a basis for inducement liability.”).

[REDACTED]

[REDACTED]

In practice, apremilast is often administered as part of a combination psoriasis treatment regime. Hwang Depo. Tr. at [33:1-24]; Ex. E1, Pharmascience’s CFN at ¶¶ 42-52; DTX Pharma-004; DTX Pharma-009; DTX Pharma-005; DTX Pharma-008; JTX-0273. Extensive medical literature discusses the use of apremilast as part of a combination therapy. Ex. E1, Pharmascience’s CFN at ¶¶ 45-51; DTX Pharma-004; DTX Pharma-008; JTX-0273; DTX Pharma-009; DTX Pharma-004.

Clinicians often use apremilast “in [combination therapy] to reduce residual [plaque psoriasis] that is not adequately controlled with another treatment alone.” DTX Pharma-008 at DTX-Pharma-008.0001; JTX-0273 at JTX-273\_5-JTX-273-6 (“[a]mong the 81 patients who were treated with apremilast, combination therapy was used at some point in 43 of these patients”); DTX Pharma-009 at DTX-Pharma-009.0003-DTX-Pharma-009.0004. Apremilast is thus widely understood to be *more* effective as a combination therapy than as a monotherapy. Ex. E1, Pharmascience’s CFN at ¶ 51; DTX Pharma-004 at DTX-Pharma-004.0001.

Accordingly, this use of apremilast as part of combination therapy is substantial. *See Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1327 (Fed. Cir. 2009) (holding that a common and deliberate use outside the scope of the claims is a substantial non-infringing use for purposes of indirect infringement). [REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

The claims, however, recite a method of treating psoriasis consisting of administering stereometrically pure apremilast. Ex. E1, Pharmascience's CFN at ¶ 63; JTX-0013. In other words, the claims expressly *preclude* any methods that include other psoriasis treatment steps, compositions, or therapies. Ex. E1, Pharmascience's CFN at ¶¶ 65-67. Indeed, Application No. 14/826,027 (which issued at the '541 patent) originally contained 61 claims, including claims directed to “[a] method of treating . . . psoriasis . . . which *comprises* orally administering . . . stereomerically pure [apremilast]” *Id.* at ¶ 57; JTX-0024 at JTX-24\_5-JTX-24-74 (Aug. 13, 2015 Patent Filing) at Claim 1 (emphasis added); *see also id.* at Claims 2, 33. The application also included claims directed to combination therapy that included “administering to the patient a therapeutically effective amount of one or more second active agents” commonly used in the treatment of psoriasis. Ex. E1, Pharmascience's CFN at ¶¶ 58-59; JTX-0024 at JTX-24\_56-JTX-24-64 (Aug. 13, 2015 Patent Filing at Claim 19).

The PTO Examiner rejected the original claims, citing to lack of novelty under § 102 and obviousness under § 103 in light of the prior art. *See e.g.*, Ex. E1, Pharmascience's CFN at ¶ 60; JTX-0024 at JTX-24\_99-JTX-24\_120 (Aug. 30, 2016 Non-Final Rejection). The patent applicant cancelled those claims and submitted new claims that replaced the original “comprises” claim language with “consisting of” and eliminated claims to combination therapy. Ex. E1, Pharmascience's CFN at 61-64; JTX-0024 at JTX-24\_1146-JTX-24\_1174 (May 03, 2018 Amendment) . In making this amendment, the applicant confirmed: “The transitional phrase ‘consisting of’ excludes any element, step, or ingredient not specified in the claim. *In re Gray*, 53 F.2d 520, 11 USPQ 255 (CCPA 1931). In each of these claims, the method of treating the recited

disease consists of an initial titration dosing schedule, which itself consist of five (5) steps over five (5) days.” JTX-0024 at JTX-24\_1146-JTX-24\_1174 (May 03, 2018 Amendment). The applicant thus confirmed its understanding that the first “consisting of” limited “the method of treating the recited disease [i.e., psoriasis]” and the second “consisting of” limited the “initial titration dosing schedule.” This prosecution history confirms that the claims as issued expressly and intentionally preclude administration of apremilast as part of a combination therapy. Ex. E1, Pharmascience’s CFN at ¶¶ 65-67. In adding *two* “consisting of” terms, the applicant not only deliberately limited the titration dosing schedule, but also “exclude[d] any element, step, *or ingredient* not specified in the claim” for “the method of treating the recited disease [i.e., psoriasis]” JTX-0024 at JTX-24\_1169-JTX-24\_1170 (emphasis added). Amgen should not now be heard to argue otherwise.

Because Pharmascience’s label does not encourage administration of Pharmascience’s ANDA product as only a monotherapy (as opposed to part of a combination psoriasis treatment regime that includes *other* ingredients and steps as part of the method of treating psoriasis), Pharmascience does not induce infringement of the claims. Likewise, the use of Pharmascience’s ANDA product as part of a combination psoriasis treatment regime is a substantial non-infringing use that precludes Pharmascience from contributorily infringing the asserted claims.

**2. Pharmascience’s Label Requires that the Finished Dosage Form (Including Other Ingredients) Is to be Administered Rather Than Solely Stereometrically Pure Apremilast.**

Pharmascience’s prescribing information does not contemplate the active pharmaceutical ingredient apremilast being administered alone. Pharmascience’s prescribing information only recommends administration of apremilast as a tablet that includes both the active pharmaceutical ingredient (apremilast) and [REDACTED] Ex. A1, Stipulated Facts RDP at ¶¶ 42,

45-46. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The inclusion of these additional ingredients precludes the strict “consisting of” limitation from reading on Pharmascience’s product. Ex. E1, Pharmascience’s CFN at ¶¶ 65, 111-112. Indeed, “consisting of” (unlike the more permissive “consisting essentially of” does not even permit additional ingredients that do not affect the basic and novel properties of the composition. *See PPG Industries v. Guardian Industries*, 156 F.3d 1351, 1354 (Fed. Cir. 1998) (comparing the phrases “consisting of” and “consisting essentially of”). Amgen’s arguments that the additional ingredients in Pharmascience’s finished dosage form are standard inert ingredients thus has no legal relevance to the strict application of the “consisting of” claim language.

Because Pharmascience’s label does not encourage administration of apremilast alone (as opposed to part of a finished dosage form with other ingredients), Pharmascience does not induce infringement of the claims. Likewise, the use of Pharmascience’s finished ANDA product is a substantial non-infringing use that precludes Pharmascience from contributorily infringing the asserted claims.

**3. Pharmascience’s Label Recommends that At Least Some Patients Follow a Different Dosage Schedule than that Recited in Claim 2**

The second use of “consisting of” in the claim language limits the method of psoriasis treatment to a single set dosage titration schedule with specific amounts of apremilast administered

at specific times of day over the course of 5 days. [REDACTED]

[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Because Pharmascience's label recommends, for at least some patients, administration of Pharmascience's ANDA Product according to an unrecited dosing titration schedule, Pharmascience does not induce infringement of the claims. Likewise, the administration of Pharmascience's ANDA product according to one of these unrecited dosing schedules is a substantial non-infringing use that precludes a finding of contributory infringement.

**b. Amgen's Expert Failed to Consider the "Consisting of" Limitations in His Infringement Analysis**

Amgen's expert, Dr. Alexis, submitted an opinion in his opening report that Pharmascience's product infringed the asserted claims, even though he admitted that he did not consider the effect of the "consisting of" limitations in that analysis. Importantly, it is *not* the case that Dr. Alexis properly considered the "consisting of" terms but did not explain it in his expert report because he did not realize there was a dispute over the limitation—he did not perform any analysis of the "consisting of" limitation at all.

At his deposition Dr. Alexis conceded that he did not include any analysis of the "consisting of" limitations in his opinion, and could not even answer what he understood those terms to mean in forming his opinion:

Q. When you reviewed and signed your November 24 report, did you understand the transitional phrases "comprises" and "consisting of" to mean different things in a patent claim?

A: Unless I specifically opined on that question, that specific question and included it in my report, I cannot give you an accurate, precise, or truthful answer. So if it's in my report, I would be happy to refer to it and refresh my memory, but I don't recall specifically opining on the differences of these phrases. But my opinions on the language contained in claim 1 of '243, among other claims that we have that I've listed in my report, my opinions are as I've documented them.

Q. How can you opine that Pharmascience infringes claims that use the “consisting of” transitional phrase when you’re not sure what that phrase means in a patent claim?

A: I did not -- just for the record, I did not say I didn’t understand what “consisting of” or “comprising of” or any other words in the claim mean.

Q. Okay. What did you understand “consisting of” to mean when you reviewed and signed your November 24 report?

A: To be able to answer your question precisely and accurately, I would have had to document what my opinion or interpretation of that particular question is, and I don’t think I have that in my report. Therefore, I can’t tell you with certainty.

Alexis Dep. Tr. at [85:2-86:14].

Thus, Dr. Alexis’s opinion on the “consisting of” limitations is entitled to no weight. Without competent expert testimony on this fact-intensive issue, Amgen cannot satisfy its burden of proof on infringement.

**E. The ’283 Patent<sup>4</sup>**

**i. The Asserted Claims of the ’283 Patent**

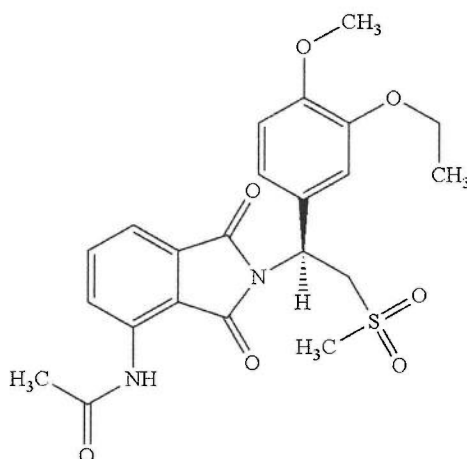
Claim 2 of the ’283 patent is directed to the crystal Form A of enantiomerically pure apremilast, comprising five XRPD peaks. Claim 27, which depends from claim 2, is directed to a solid pharmaceutical composition comprising the crystal form of claim 2.

Asserted claims 2 and 27, and the claims from which they depend, read:

1. An unsolvated crystal form of the compound of Formula (I):

---

<sup>4</sup> The ’283 patent has only been asserted against Defendant Zydus.



which is enantiomerically pure, wherein the crystal form is Form A, which has an X-ray powder diffraction pattern comprising peaks at about 8.1, 14.4, 17.4, 23.6 and 25.1 degrees  $2\theta$ , or Form F, which has an X-ray powder diffraction pattern comprising peaks at about 8.1, 15.6, 17.3, and 25.4 degrees  $2\theta$ .

2. The crystal form of claim 1, wherein the crystal form is Form A, which has an X-ray powder diffraction pattern comprising peaks at about 8.1, 14.4, 17.4, 23.6 and 25.1 degrees  $2\theta$ .

27. A solid pharmaceutical composition comprising the crystal form of claim 2.

JTX-0006 at claims 1, 2, and 27.

**ii. The '283 patent is invalid as anticipated and/or obvious.**

The '052 publication, the published application from which all of the asserted patents (other than the '541 patent) derive from, renders the '283 patent invalid as anticipated and/or obvious. By choosing to prosecute the '283 patent as a continuation-in-part in the same family as the '052 publication, it is undisputed that the portion of the '283 patent's specification that was published in the '052 publication (and appears in the '638 and '536 patents) became prior art to '283 patent claims. Thus, the same passages in the '052 publication that supported Celgene's claims to "stereomerically pure apremilast" in the '638 and '536 patents also serve to invalidate the related claims to enantiomerically pure crystalline apremilast Form A in the '283 patent.

**iii. The '052 publication anticipates claims 2 and 27 of the '283 patent.**

The '283 patent specification expressly teaches only one method for making crystalline apremilast Form A, namely crystallizing apremilast from solutions of ethanol, acetone, or mixtures thereof by fast cooling. (JTX-6 ('283 patent) at 39:17-40:46 (Example 2).) Both the '052 publication and '283 patent contain a single example for making stereomerically pure apremilast, which concludes by crystallizing from a mixture of ethanol and acetone. (*Id.*; DTX-179 ('052 publication) at ¶¶ 96-103.) In other words, practicing the single example for making stereomerically pure (*i.e.*, enantiomerically pure) apremilast taught in both the '052 publication and the '283 patent would inherently and necessarily result in formation of crystalline apremilast Form A.

Claim 2 of the '283 patent is directed to enantiomerically pure crystalline apremilast Form A containing five specified XRPD peaks. Claim 27 depends from claim 2 and is directed to a pharmaceutical composition comprising the crystal form of claim 2. The experts agree that if a POSA possesses enantiomerically pure crystalline apremilast Form A, any sample would inherently and necessarily demonstrate all five specified XRPD peaks listed in claim 2. (PTO at ¶¶ 156-57.) It is also undisputed that the '052 publication and '283 patent contain the same teachings as to formulating stereomerically or enantiomerically pure apremilast into pharmaceutical compositions. (JTX-6 ('283 patent) at 4:10-22, 9:57-10:10, 32:28-38:52; DTX-179 ('052 publication) at ¶¶ 10, 27, 59-94.)

Thus, the only dispute between the parties is whether the process of Example 2, set forth in the '052 publication and repeated in the '283 patent, would yield crystalline apremilast Form A. Zydus's expert, Dr. Mark Sacchetti, will explain that the procedures set forth in Example 2 require heating the solution of ethanol and acetone to reflux but do not specify the conditions for cooling during the crystallization. A POSA would understand this process to teach fast cooling, *i.e.* heating

a sample to reflux and then allowing it to cool to room temperature naturally over the course of one to two hours. Dr. Sacchetti will testify that if the cooling method was different, such as using an apparatus to control how quickly the solution would cool, *i.e.* slow cooling, a POSA would expect such details to be included within the written procedure. Thus, based on the explicit teachings in the '283 patent, Example 2 must inherently result in the formation of enantiomerically pure crystalline apremilast Form A.

Amgen's expert, Dr. Myerson, will argue that several third parties conducted similar experiments while opposing the European equivalent of the '101 patent, and represented to the European Patent Office that fast cooling under the Example 2 procedure yields crystalline apremilast Form B and not Form A. Regardless of the fact that both experts agree that no single third-party experiment accurately practiced the entirety of Example 2, Amgen persists that these experiments render the '283 patent claims not anticipated. In essence, by arguing that fast cooling in the process of Example 2 does not yield crystalline apremilast Form A, Amgen is representing to the Court that its teachings for making Form A in the '283 patent are inaccurate and that the claimed inventions are not fully enabled or described. That would render claims 2 and 27 of the '283 patent invalid under 35 U.S.C. § 112 for lack of enablement and/or written description as opposed to anticipation. Of course, Amgen cannot escape an invalidity challenge (anticipation) by arguing its own patent is invalid for a different reason (enablement) simply because Zydus has not raised enablement as an alternate basis for invalidity. Amgen's patent must satisfy the requirements of both 35 U.S.C. §§ 102 and 112 in order to be valid. Zydus cannot be expected to have foreseen that Amgen would admit that its own patent is invalid for lack of enablement.

Zydus has never advanced Section 112 defenses because Dr. Sacchetti, in accordance with the understanding of any POSA, has assumed the teachings in the '283 patent specification to be

accurate under the patentee's duty of candor to the United States Patent and Trademark Office and the public at large when obtaining their patent monopoly. 37 C.F.R. § 1.56. Like Dr. Sacchetti, the Court must also assume the teachings of the patent to be true, unless shown by an opponent to be inaccurate by clear and convincing evidence. 35 U.S.C. § 282(a); *see also Microsoft Corp. v. I4I Ltd. P'ship*, 564 U.S. 91, 95 (2011). In fact, when arguing Zydus infringes the '101 (Form B) patent, Amgen made its reference sample of Form A by fast cooling apremilast in a mixture of ethanol and acetone consistent with the very teachings of the '283 patent that Amgen now seeks to rewrite for its own convenience.

Thus, claims 2 and 27 of the '283 patent are invalid for anticipation by the '052 publication.

**iv. Claims 2 and 27 of the '283 Patent Would Have Been Obvious Over the '052 Publication in View of Fieser, Guillory, and Byrn 1994 and the Knowledge of a POSA.**

In addition to being anticipated by the '052 publication, the '283 patent also would have been obvious to a person of ordinary skill in the art based on the '052 publication's teachings in view of the teachings of Fieser, Guillory, and Byrn 1994. Based on these three additional references, a POSA would have been not only motivated to crystallize enantiomerically pure apremilast in a mixture of ethanol and acetone, but would have utilized a fast cooling technique that inherently results in crystalline apremilast Form A with the XRPD peaks set forth in claim 2 of the '283 patent.

Dr. Sacchetti will testify that based on the teachings in the '052 publication, a POSA would have been motivated with a reasonable expectation of success to produce enantiomerically pure crystalline apremilast for pharmaceutical use, including formulating that same enantiomerically pure crystalline apremilast into a pharmaceutical composition. A POSA would have understood that enantiomerically pure crystalline apremilast could be prepared by the process set forth in Example 2, even though the cooling rate for crystallization is not specified.

Dr. Sacchetti will explain that a POSA would have been motivated to conduct the crystallization or recrystallization using the routine, common methods and techniques for crystallizing a solid from a single solvent or mixture of solvents, such as those taught in Fieser, Guillory, and Byrn 1994. From these three references, a POSA would have understood that recrystallization could be accomplished from a solvent or mixture of solvents via fast cooling, slow cooling, or evaporation, and that varying cooling rates could result in different polymorphs. As Dr. Sacchetti will note, each of these techniques would have been well known to a POSA from the POSA's own education, knowledge, and experience and could have been carried out in a routine fashion.

Dr. Sacchetti will also testify that in light of the combined teachings of the '052 publication, Fieser, Guillory, and Byrn 1994, a POSA would have been motivated to use different rates of cooling, including fast cooling, with the process taught in Example 2 and would have reasonably expected to succeed in producing enantiomerically pure crystalline apremilast, which would inherently be Form A. That POSA would have been further motivated to formulate enantiomerically pure crystalline apremilast Form A to make a pharmaceutical composition for use in treating various diseases with a reasonable expectation of success based on the teachings in the '052 publication.

Amgen and its expert, Dr. Myerson, will fail to rebut Dr. Sacchetti's opinions concerning obviousness on these grounds. Dr. Myerson concedes that a POSA would have been motivated by the '052 publication to use ethanol and acetone to obtain enantiomerically pure crystalline apremilast, and would have reasonably expected to succeed in those efforts using fast cooling. His only disagreement is that using fast cooling in the process of Example 2 would result in Form B and not Form A based on the same third-party experiments he relies on when trying to rebut

anticipation. But once again, Amgen and Dr. Myerson may not evade invalidity by offering evidence that contradicts the explicit teachings about how to make crystalline apremilast Form A in Amgen's own '283 patent that were confirmed by Amgen's own Form A reference sample. 35 U.S.C. § 282(a) ("a patent shall be presumed valid"); 37 C.F.R. § 1.56 ("Duty to disclose information material to patentability.").

Otezla does not contain crystalline apremilast Form A, therefore there can be no nexus to objective indicia. Since Amgen cannot advance objective indicia with respect to the '283 patent, the clear and convincing evidence of *prima facie* obviousness will stand un rebutted. Thus, claims 2 and 27 of the '283 patent are invalid as obvious over the '052 publication in view of Fieser, Guillory, and Byrn 1994 and the knowledge of a POSA.

**v. Claims 2 and 27 of the '283 Patent Would Have Been Obvious Over the '358 Patent in view of Byrn 1995, in Further View of Guillory and Byrn 1994 and the Knowledge of a POSA**

Claims 2 and 27 of the '283 patent also would have been obvious based on the teachings of the '358 patent in view of the teachings of Byrn 1995, in further view of teachings from Guillory and Byrn 1994 and the knowledge of a POSA.

Dr. Sacchetti, Dr. Steed, and Dr. Gribble will all testify that the '358 patent discloses enantiomerically/stereomerically pure apremilast. Dr. Sacchetti will explain that given the '358 patent's disclosure of pharmaceutical utility, a POSA would have been motivated by teachings in Byrn 1995 to ensure control of the crystal form of apremilast by conducting a polymorph screen using various solvents, including ethanol, acetone, and mixtures thereof and then analyze the resulting crystals by XRPD.

Dr. Sacchetti will further testify that a POSA would have been motivated to look to Guillory and Byrn 1994, which teach general techniques for undertaking a polymorph screen. Such a polymorph screen would have included crystallization from a single solvent or mixture of solvents,

by a variety of different cooling rates (*e.g.*, fast cooling, slow cooling, and evaporation). As a result of this screen, a POSA would have obtained enantiomerically pure crystalline apremilast Form A that when analyzed by XRPD would have inherently possessed the XRPD peaks set forth in claim 2 of the '283 patent.

Dr. Myerson will testify that Form A was not obvious because, according to Dr. Davies, the '358 patent does not disclose enantiomerically pure apremilast and there was no reason to select apremilast for further study over the other compounds taught by the '358 patent. As discussed above, neither the facts nor the legal authority support Dr. Myerson's and Dr. Davies' theories based on an improper lead compound analysis. Rather, once the '358 patent disclosed enantiomerically pure apremilast, Byrn 1995, Guillory and Byrn 1994, which the experts agree were well-known in the art, would have rendered Form A and other polymorphs obvious.

Thus, as Dr. Sacchetti will conclude, in light of the combined teachings of the '358 patent, Byrn 1995, Guillory, and Byrn 1994, a POSA would have been motivated to subject enantiomerically pure apremilast to a polymorph screen that crystallizes apremilast from ethanol, acetone, and/or mixtures thereof, by methods that include fast cooling, and would have reasonably expected to succeed in producing enantiomerically pure crystalline apremilast that, based on the '283 patent's own disclosure, would have been crystalline apremilast Form A. That POSA would have been further motivated to formulate that enantiomerically pure crystalline apremilast Form A to make a pharmaceutical composition for use in treating various diseases with a reasonable expectation of success based on the teachings in the '358 patent's teaching of pharmaceutical compositions containing the various exemplified compounds.

Since Amgen cannot advance objective indicia with respect to the '283 patent, the clear and convincing evidence of *prima facie* obviousness will stand un rebutted. Thus, claims 2 and 27

of the '283 patent are invalid as obvious over the '358 patent in view of Byrn 1995, in further view of Guillory and Byrn 1994 and the knowledge of a POSA.

## V. CONCLUSION

The evidence will show that all Asserted Claims are invalid for anticipation, obviousness, obviousness-type double patenting, and/or lack of written description and enablement. It will also be clear from the evidence that Amgen has not met, and cannot meet, its burden to show that Pharmascience will infringe the asserted claims of the '541 patent or that Zydus will infringe the asserted claims of the '101 patent.

Dated: June 1, 2021

By: /s/ Lisa J. Rodriguez

Lisa J. Rodriguez  
(ljrodriguez@schnader.com)  
**SCHNADER HARRISON SEGAL &  
LEWIS LLP**  
Woodland Falls Corporate Park  
220 Lake Drive East, Suite 200  
Cherry Hill, NJ 08002-5222  
(856) 482-5222

Of Counsel:

Dennies Varughese  
(dvarughese@sternekessler.com)  
Deirdre M. Wells  
(DWELLS@sternekessler.com)  
Dallin Glenn (DGLENN@sternekessler.com)  
**STERNE, KESSLER, GOLDSTEIN &  
FOX P.L.L.C**  
1100 New York Avenue NW, Suite 600  
Washington, D.C. 20005  
(202) 371-2600

*Attorneys for Defendant Pharmascience Inc.*

By: /s/ Eric I. Abraham

Eric I. Abraham (eabraham@hillwallack.com)  
**HILL WALLACK LLP**  
21 Roszel Road  
Princeton, NJ 08540  
(609) 924-0808

Of Counsel:

George Lombardi (GLombardi@winston.com)  
Maureen Rurka (MRurka@winston.com)  
Samantha M. Lerner (SLerner@winston.com)  
**WINSTON & STRAWN LLP**  
35 W. Wacker Drive  
Chicago, IL 60601  
(312) 558-5600

Jovial Wong (JWong@winston.com)  
Sharon Lin (SLin@winston.com)  
**WINSTON & STRAWN LLP**  
1901 L Street NW  
Washington, D.C. 20036  
(202) 282-5000

Noorossadat Torabi (NTorabi@winston.com)  
**WINSTON & STRAWN LLP**  
101 California Street, Fl. 34  
San Francisco, CA 94111

(415) 591-1000

*Attorneys for Defendants Dr. Reddy's  
Laboratories, Inc., Dr. Reddy's Laboratories,  
Ltd, and Sandoz Inc.*

By: /s/ Theodora McCormick

Theodora McCormick  
(tmccormick@ebglaw.com)  
Lauren B. Cooper (lcooper@ebglaw.com)  
Robert Lufrano (rlufrano@ebglaw.com)  
**EPSTEIN BECKER & GREEN, P.C.**  
150 College Road West, Suite 301  
Princeton, NJ 08540  
(609) 455-1540

*Of Counsel:*

Michael J. Gaertner  
(MGaertner@lockelord.com)  
David B. Abramowitz  
(DAbramowitz@lockelord.com)  
Carolyn A. Blessing  
(cblessing@lockelord.com)  
Emily L. Savas (esavas@lockelord.com)  
Jennifer M. Coronel  
(Jennifer.Coronel@lockelord.com)  
August Melcher  
(august.melcher@lockelord.com)  
**LOCKE LORD LLP**  
111 South Wacker Drive  
Chicago, IL 60606  
(312) 443-0700

*Attorneys for Defendant Zydus  
Pharmaceuticals (USA) Inc.*

**CERTIFICATION OF SERVICE**

The undersigned attorney certifies that a copy of the foregoing **DEFENDANTS' PRETRIAL BRIEF** was served by notice of electronic filing on the 1st day of June 2021, upon all counsel of record.

Dated: June 1, 2021

By: /s/ Eric I. Abraham

Eric I. Abraham  
(eabraham@hillwallack.com)